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Illness severity and risk of mental morbidities among patients recovering from COVID-19: a cross-sectional study in the Icelandic population

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**Illness severity and risk of mental morbidities among patients recovering from COVID-19:
a cross-sectional study in the Icelandic population**

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Abstract

Objective

To test if patients recovering from COVID-19 are at increased risk of mental morbidities and to what extent such risk is exacerbated by illness severity.

Design

Population-based cross-sectional study.

Setting

Iceland.

Participants

A total of 22,861 individuals were recruited through invitations to existing nationwide cohorts and a social media campaign from April 24 to July 22 2020, of which 373 were patients recovering from COVID-19.

Main outcome measures

Symptoms of depression (Patient Health Questionnaire [PHQ-9]), anxiety (General Anxiety Disorder Scale [GAD-7]), and PTSD (modified Primary Care PTSD Screen for DSM-5 [PC-PTSD-5]) above screening thresholds. Adjusting for multiple covariates and comorbidities, multivariable Poisson regression was used to assess the association between COVID-19 severity and mental morbidities.

Results

Compared to individuals without a diagnosis of COVID-19, patients recovering from COVID-19 had increased risk of depression (22.1% vs. 16.2%; aRR 1.48, 95% CI 1.20 to 1.82) and PTSD (19.5% vs.

15.6%; aRR 1.38, 95% CI 1.09 to 1.75) but not anxiety (13.1% vs. 11.3%; aRR 1.24, 95% CI 0.93 to 1.64). Elevated relative risks were limited to recovering COVID-19 patients 40 years or older and were particularly high among patients 60 years or older. Among recovering COVID-19 patients, symptoms of depression were particularly common among those in the highest, compared to the lowest tertile of flu-like symptom burden (47.1% vs. 5.8%; aRR 6.42, 95% CI 2.77 to 14.87), among patients confined to bed for seven days or longer compared to those never confined to bed (33.3% vs. 10.9%; aRR 3.67, 95% CI 1.97 to 6.86), and among patients hospitalized for COVID-19 compared to those never admitted to hospital (48.1% vs. 19.9%; aRR 2.72, 95% CI 1.67 to 4.44).

Conclusions

Severe disease course is associated with increased risk of depression and PTSD among patients recovering from COVID-19.

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Strengths and limitations of this study

- To our knowledge, this is the first study addressing mental morbidities among recovering COVID-19 patients in a general population setting, including outpatients.
- This study includes more than 20% of all patients diagnosed with COVID-19 by RT-PCR during the first wave of the epidemic in Iceland, where the diagnostic rate was among the highest worldwide, allowing us to perform sensitivity analyses limited to individuals who all had been screened for SARS-CoV-2.
- The extensive and well-piloted questionnaire allowed us to obtain validated symptom assessment of mental morbidities along with detailed information on flu-like symptom burden for all individuals during the flu season in Iceland.
- The cross-sectional design is less informative on the directionality of the studied associations, and as the study is nested within a small, economically and socially secure society, the generalizability of the findings may be limited.
- It is possible that individuals with severe symptoms of depression and anxiety were more likely to report high levels of flu-like symptoms during the preceding two months when responding to the questionnaire, yielding a outcome-dependent misclassification.

INTRODUCTION

With almost 100 million reported cases and 2.2 million deaths globally,[1] the coronavirus disease 2019 (COVID-19) pandemic remains a major public health challenge worldwide. Beyond the extensive socioeconomic impact and suffering of patients during the illness, there are rising concerns about long-term somatic and psychological impact on recovering patients.[2-6]

Mental health consequences among patients in recent epidemics are well documented.[7, 8] With respect to COVID-19, a meta-analysis of 31 studies suggested a 45-47% pooled prevalence of mild to severe symptoms of depression and anxiety in patients with COVID-19, mostly inpatients.[9] Moreover, extreme rates of posttraumatic stress have been reported among COVID-19 inpatients in China.[10, 11] Previous studies are mostly small, limited to inpatients, and rarely include a control group. Few studies have reported symptoms of mental morbidities after recovery from COVID-19 with existing data suggesting high levels of symptoms[12] and elevated rates of diagnosed psychiatric disorders among COVID-19 inpatients during the first weeks after hospital discharge.[13] Flu-like symptoms, such as myalgia, cough and sore throat, have been associated with mental morbidities in the general population during the COVID-19 pandemic.[14, 15] To what extent flu-like symptoms are associated with psychological distress in recently recovered COVID-19 patients remains unknown.

The first wave of COVID-19 in Iceland started on February 28. Through modest but systematic mitigation strategies[16] the incidence of COVID-19 had effectively been attenuated by the end of April 2020, with only sporadic cases occurring until the onset of the second wave of infections on July 22. During this period, more than 20% of the total population was tested using reverse transcription-polymerase chain reaction (RT-PCR); a total of 1820 tested positive for SARS-CoV-2 (0.5% of the total population), of whom 113 were hospitalized (6%), and ten died (0.5%).[17] Here

we explore mental health indicators in patients recovering from COVID-19 in the first wave of the pandemic and the potential role of disease severity on the risk of mental morbidities.

METHODS

Study population and design

The COVID-19 National Resilience Cohort was established on April 24, 2020, with the overarching aim of understanding the long-term public health impact of the COVID-19 epidemic in Iceland.[18] Eligible were all Icelandic and English speaking individuals 18 years or older who had an Icelandic electronic ID (total population ≥ 18 years on January 1, 2020 was 282,770[19]). Recruitment was mainly through social media and public media coverage, though participants in ongoing cohort studies (The SAGA cohort [N = 31,795 women]; iStopMM [N = 80,730 men and women], and Health and well-being of Icelanders [N = 6,102 men and women]) received email or postal invitations to participate. In addition, all individuals in Iceland who tested positive by RT-PCR for SARS-CoV-2 through May 2020 (N = 1,800) received a text message invitation, on June 3, 2020. All participants signed an electronic informed consent and subsequently answered a web-based questionnaire. The study was approved by the National Bioethics Committee (NBC no. 20-073) and the Data Protection Authority.

We performed a cross-sectional analysis of participants responding to the baseline questionnaire from April 24 through July 22, 2020. A total of 22,680 individuals had participated at that time point. We excluded individuals who did not state whether or not they had undergone a diagnostic test (n = 989) or been diagnosed with COVID-19 (n = 19), and those who did not answer all questions on flu-like symptoms (n = 762) or all items in any one of the three measures of depression, anxiety and posttraumatic stress (n = 49) (see supplementary Figure 1). The final analytic sample consisted of 20,861 participants.

Measures

Sociodemographic and health-related factors

Sociodemographic information included the date of response to the baseline questionnaire, gender, age, education, average monthly income during the past year, relationship status, and residency (capital vs. other regions). We defined relationship status as either being in a relationship (married, cohabiting, or in a relationship yet not cohabiting) or not (single, widowed or divorced). Highest level of education was defined as 1) compulsory; 2) upper secondary/vocational/other; 3) university exam (bachelor's degree or diploma certificate); or 4) master's or doctoral degree. Monthly income categories were defined as 1) low income, <1.653 GBP; 2) low-medium income, 1.653-2.755 GBP; 3) medium income, 2.756-3.858 GBP; 4) medium-high income, 3.859-5.511 GBP; 5) high income, >5.511 GBP (conversion rates according to The Central Bank of Iceland, April 24, 2020[20]).

Health-related information included current smoking status (yes/no), binge drinking during the past two months (defined as ≥ 4 drinks for women and ≥ 5 drinks for men or other genders[21]), a previous diagnosis of a psychiatric disorder (made by physicians or psychologists; yes/no), and previous diagnosis of somatic comorbidities including hypertension, diabetes, heart disease, lung disease, chronic kidney disease, cancer, and immunosuppressive state or immunosuppressive therapy (none, one, or two or more comorbid conditions). Additionally, participants reported their height (m) and weight (kg), which was used to estimate body mass index (BMI) as kg/m^2 .

Diagnosis of COVID-19 and illness severity

We asked participants if they had been tested for COVID-19 regardless of testing method. If they responded yes, we asked if they had been diagnosed with COVID-19, and if so, how long ago they had been diagnosed, how long they were confined to bed due to COVID-19, and whether they had been hospitalized.

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As the first wave of COVID-19 coincided with the flu season in Iceland, we asked all participants how many days they had experienced nine specific flu-like symptoms over the preceding two months. The symptoms, previously identified as relevant for COVID-19,[22, 23] were: fever, cough, sore throat, impaired sense of taste or smell, headache, myalgia (body aches), gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), shortness of breath, fatigue and weakness. Response options were: “never”, “1-2 days”, “3-6 days”, “1-2 weeks”, and “more than 2 weeks”, which were scored from “0” (never) to “4” (≥ 2 weeks). We calculated flu-like symptom burden by summing all symptom scores indicated by each participant (range 0-36 points) and then divided scores into tertiles of the distribution within the COVID-19 cohort (lowest 0-11, mid 12-23, highest 24-36 points).

Symptoms of mental illness

We used the 9-item-Patient Health Questionnaire (PHQ-9) to measure symptoms of depression with the recommended cut-off of ≥ 10 points serving as a screening indicator for depression in an adult primary care sample.[24] We used the 7-item Generalized Anxiety Disorder scale (GAD-7) to assess symptoms of anxiety. A cut-off of ≥ 10 was employed as an indicator of moderate to severe symptoms of a generalized anxiety disorder in an adult primary care sample.[25] The 5-item Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) was used to measure symptoms of posttraumatic stress,[26] with a modified version tailored to COVID-19 (*e.g.*, “Had nightmares about COVID-19?”). We scored the responses as “0” (never) or “1” (seldom, sometimes, often, very often) with a total score ranging from 0-5. We defined COVID-19-specific PTSD as a PC-PTSD-DSM-5 score of ≥ 4 , which has previously been reported as optimal.[26]

Statistical analysis

First, we contrasted the distribution of sociodemographic and health-related factors between individuals with and without a COVID-19 diagnosis. We then ran univariable and multivariable linear

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3 regression to detect potential differences in continuous symptoms of depression (PHQ-9), anxiety
4 (GAD-7) and PTSD (PC-PTSD-5) across groups with and without a confirmed COVID-19 diagnosis. We
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6 used robust (modified) Poisson regression, with the classical sandwich estimator,[27] to determine
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8 the association between a confirmed diagnosis of COVID-19 and risk of depression, anxiety, or PTSD
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10 surpassing cut-offs of potential clinical significance. The association is presented as unadjusted and
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12 adjusted relative risks (aRRs) with 95% confidence intervals (CIs) and as prevalence differences. All
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14 multivariable models included age (continuous), gender (male, female, or other), educational level
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16 (classification described above), income (continuous), current smoking (yes/no), previous diagnosis
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18 of a psychiatric disorder (yes/no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and
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20 the time period of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May
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22 24-July 22). We then performed these analyses stratified by sex and age (18-39, 40-59, 60 years or
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24 older).

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32 We performed several sensitivity analyses. As we were concerned for a potential overlap between
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34 physical symptoms of COVID-19 and some items on the mental health assessments (e.g. fatigue), we
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36 performed a sensitivity analysis excluding COVID-19 patients diagnosed within 14 days of responding
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38 to the questionnaire. We further, reran the analysis using individuals tested but not positive for
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40 COVID-19 as a control group. Finally, as our primary Poisson regression analysis included individuals
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42 with complete responses to PHQ-9 (n = 18,822), GAD-7 (n = 19,163) and PC-PTSD-5 (n = 17,562), we
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44 repeated these analyses, including the entire analytic sample (n = 20,861), using multiple imputation
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46 by creating 10 imputed data sets with 10 iterations each.[28]

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52 Limited to individuals diagnosed with COVID-19, we used multivariable Poisson regression to
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54 evaluate the association between indicators of COVID-19 severity and mental morbidities. Adjusting
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56 for the same covariates as listed above, we explored the association between time confined to bed
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due to COVID-19 (never vs. 1-6 days or 7 days or more), flu-like symptom burden (in tertiles) and whether or not patients had been hospitalized, and mental morbidities among recovering patients.

Next we compared the proportion of individuals with and without COVID-19 (tested and not tested for SARS-CoV-2) who reported each of nine flu-like symptoms for one week or more. We used robust Poisson regression to calculate unadjusted and multivariable-adjusted relative risks of each symptom among individuals tested vs. not tested for SARS-CoV-2, and then diagnosed vs. not diagnosed with COVID-19. The multivariable models included the same covariates as listed above. Using linear regression, we then tested the association between flu-like symptom burden and mental morbidities both among individuals with and without a diagnosis of COVID-19 (tested and not tested for SARS-CoV-2). We then tested whether flu-like symptoms mediated the association between a confirmed COVID-19 diagnosis and mental morbidities by adding flu-like symptoms to the multivariable models. All analyses were conducted in R (Version 3.6.2)

Patient and public involvement

No patients were involved in putting forward the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. Dissemination of the results to study participants and the Icelandic population will be obtained through a media outreach (e.g., press release and communication on our study website) on publication of this study.

RESULTS

Background characteristics

Of the 20,861 participants, 5,419 individuals had been tested for SARS-CoV-2, of whom 373 reported having been diagnosed with COVID-19 (97.9% more than two weeks before responding to the questionnaire; Table 1). Compared to other participants, individuals previously diagnosed with COVID-19 were younger (mean age: 48.3 vs. 54.8 years), had a higher educational level and income

and were more likely to binge drink alcohol. They were furthermore less likely to be current smokers and have previously been diagnosed with psychiatric disorders or somatic diseases.

Table 1: Characteristics of the study population, with and without a diagnosis of COVID-19.

	No. (%)		
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)	P-value
Gender			
Male	6133 (29.9)	121 (32.4)	.15
Female	14306 (69.8)	250 (67.0)	
Other	36 (0.2)	2 (0.5)	
Missing	13 (0.1)	0 (0)	
Age			
18-29 years	1191 (5.8)	51 (13.7)	<.001
30-39 years	1949 (9.5)	39 (10.5)	
40-49 years	3644 (17.8)	99 (26.5)	
50-59 years	5309 (25.9)	99 (26.5)	
60-69 years	5359 (26.2)	74 (19.8)	
70 years or older	3036 (14.8)	11 (2.9)	
Highest educational level			
Compulsory education	2865 (14.0)	30 (8.0)	.008
Upper secondary, vocational or other education	6303 (30.8)	117 (31.4)	
Bachelor's degree or diploma certificate	6517 (31.8)	135 (36.2)	
Master's or Ph.D. degree	4685 (22.9)	91 (24.4)	
Missing	118 (0.6)	0 (0)	
Average monthly income ^a			
Low income	3527 (17.2)	50 (13.4)	<.001
Low-medium income	5642 (27.5)	88 (23.6)	
Medium income	4993 (24.4)	82 (22.0)	
Medium-high income	3527 (17.2)	91 (24.4)	
High income	1825 (8.9)	47 (12.6)	
Missing	974 (4.8)	15 (4.0)	
Residence			
Capital area	13986 (68.3)	270 (72.4)	.18
Elsewhere in Iceland	6352 (31.0)	102 (27.3)	
Abroad	140 (0.7)	1 (0.3)	

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4	Missing	10 (0.0)	0 (0)	
5	Marital status			
6	In a relationship	15735 (76.8)	302 (81.0)	.09
7	Single	4671 (22.8)	71 (19.0)	
8	Missing	82 (0.4)	0 (0)	
9				
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11	BMI category			
12	< 25, Normal weight	5931 (28.9)	112 (30.0)	.70
13	25-30, Overweight	7931 (38.7)	138 (37.0)	
14	> 30, Obese	6127 (29.9)	118 (31.6)	
15	Missing	499 (2.4)	5 (1.3)	
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18	Smoking status			
19	No	17873 (87.2)	345 (92.5)	.002
20	Yes	2521 (12.3)	26 (7.0)	
21	Missing	94 (0.5)	2 (0.5)	
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23				
24	Binge drinking			
25	No	18255 (89.1)	312 (83.6)	.02
26	Yes	2233 (10.9)	61 (16.4)	
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29	Previous diagnosis of psychiatric disorder			
30	No	14510 (70.8)	285 (76.4)	.02
31	Yes	5776 (28.2)	84 (22.5)	
32	Missing	202 (1.0)	4 (1.1)	
33				
34	Physical diseases			
35	No comorbidities	11958 (58.4)	263 (70.5)	<.001
36	One comorbidity	5964 (29.1)	86 (23.1)	
37	2 or more comorbidities	2453 (12.0)	21 (5.6)	
38	Missing	113 (0.6)	3 (0.8)	
39				
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41	Questionnaire answer date			
42	April 24-30	7841 (38.3)	102 (27.3)	<.001
43	May 1-7	5413 (26.4)	76 (20.4)	
44	May 8-23	4999 (24.4)	53 (14.2)	
45	May 23-July 22	2235 (10.9)	142 (38.1)	
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48	Time since diagnosis			
49	Less than 2 weeks	-	8 (2.1)	-
50	2-4 weeks	-	60 (16.1)	
51	More than 4 weeks	-	305 (81.8)	
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56	^a Income categories were defined as: Low income, <1.653 GBP; Low-medium income, 1.653-2.755 GBP;			
57	Medium income, 2.756-3.858 GBP; Medium-high income, 3.859-5.511 GBP; High income, >5.511 GBP			
58	(Conversion rates according to Central Bank of Iceland, April 24, 2020)			
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^a Income categories were defined as: Low income, <1.653 GBP; Low-medium income, 1.653-2.755 GBP; Medium income, 2.756-3.858 GBP; Medium-high income, 3.859-5.511 GBP; High income, >5.511 GBP (Conversion rates according to Central Bank of Iceland, April 24, 2020)

COVID-19 and mental morbidities

Individuals diagnosed with COVID-19 reported, compared to others, higher mean scores of depression (6.11 vs. 5.07; $P < .001$) and PTSD (1.90 vs. 1.72; $P < .001$), but not anxiety (4.52 vs. 4.12; $P = 0.08$; see supplementary Table 1). Similarly, multivariable-adjusted relative risks of depression (22.1% vs. 16.2%; aRR 1.48, 95% CI 1.20 to 1.82) and PTSD (19.5% vs. 15.6%; aRR 1.38, 95% CI 1.09 to 1.75) above symptom thresholds were increased among those recovering from COVID-19 compared to others, while not on anxiety (13.1% vs. 11.3%; aRR 1.24, 95% CI 0.93 to 1.64). Risk elevations in mental morbidity in COVID-19 patients was limited to those 40 years or older and was highest among individuals 60 years or older (Table 2). Limiting the analysis to individuals who were diagnosed with COVID-19 more than two weeks before responding to the questionnaire and repeating the analysis using multiple imputation, yielded virtually identical results (see supplementary Table 2 and 3, respectively). Finally, limiting the analysis to individuals who were tested for COVID-19 generated a similar pattern yet slightly lower point estimate (see supplementary Table 4).

Table 2: The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19.

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference Crude %	Absolute difference Adjusted ^a %
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID- 19				
Depression	2992 (16.2)	75 (22.1)	1.36 (1.11 to 1.67)	1.48 (1.20 to 1.82)	5.9	8.4
Female	2421 (18.8)	56 (24.8)	1.32 (1.05 to 1.66)	1.43 (1.13 to 1.81)	6.0	8.1
Male	559 (10.0)	17 (15.2)	1.52 (0.97 to 2.37)	1.54 (0.96 to 2.47)	5.2	7.2
18-39 years	954 (33.3)	23 (27.1)	0.81 (0.57 to 1.16)	0.94 (0.65 to 1.36)	-6.2	-1.8
40-59 years	1367 (16.8)	40 (22.3)	1.33 (1.01 to 1.75)	1.72 (1.31 to 2.27)	5.5	14.7
≥60 years	671 (8.9)	12 (15.8)	1.77 (1.05 to 2.98)	2.57 (1.52 to 4.36)	6.9	21.8
Anxiety	2120 (11.3)	45 (13.1)	1.16 (0.88 to 1.53)	1.24 (0.93 to 1.64)	1.8	2.6
Female	1759 (13.4)	34 (14.8)	1.11 (0.81 to 1.51)	1.17 (0.84 to 1.62)	1.4	2.2
Male	353 (6.2)	10 (8.9)	1.43 (0.78 to 2.60)	1.39 (0.76 to 2.54)	2.6	3.0
18-39 years	770 (26.2)	13 (14.9)	0.57 (0.34 to 0.95)	0.61 (0.36 to 1.04)	-11.3	-9.3
40-59 years	951 (11.5)	27 (14.7)	1.28 (0.90 to 1.82)	1.70 (1.20 to 2.41)	3.2	10.5
≥60 years	399 (5.2)	5 (6.9)	1.31 (0.56 to 3.06)	2.13 (0.91 to 5.00)	1.7	7.5
PTSD	2699 (15.6)	59 (19.5)	1.25 (0.99 to 1.57)	1.38 (1.09 to 1.75)	3.9	7.2
Female	2198 (18.6)	46 (22.7)	1.22 (0.94 to 1.58)	1.32 (1.02 to 1.71)	4.1	6.7
Male	493 (9.1)	12 (12.1)	1.33 (0.78 to 2.27)	1.60 (0.92 to 2.77)	3.0	7.1
18-39 years	597 (24.2)	11 (15.3)	0.63 (0.37 to 1.09)	0.77 (0.45 to 1.32)	-8.9	-6.2
40-59 years	1268 (16.7)	31 (19.3)	1.15 (0.84 to 1.59)	1.36 (0.99 to 1.88)	2.6	7.8
≥60 years	834 (11.6)	17 (24.3)	2.09 (1.38 to 3.18)	2.67 (1.78 to 4.01)	12.7	27.9

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

COVID-19 illness severity and mental morbidities

In Table 3, we show the prevalence and adjusted relative risks of mental morbidities among individuals with a diagnosis of COVID-19 by number of days confined to bed, hospitalization and severity of COVID-19 symptoms. We observed dose-dependent associations between these indices of COVID-19 severity and risk of mental morbidities. Risk elevations by days confined to bed and hospitalization due to COVID-19 were statistically significant for depression and anxiety, while flu-like symptom burden was associated with all measures of psychological morbidity.

Table 3: Prevalence and adjusted relative risks (95% confidence intervals) of mental morbidities among recently recovered patients from COVID-19 by disease and symptom severity.

		Depression		Anxiety		PTSD	
	n	% ≥10 PHQ-9	aRR ^a (95%CI)	% ≥10 GAD-7	aRR ^a (95%CI)	% ≥4 PC- PTSD-5	aRR ^a (95%CI)
Confined to bed due to COVID-19							
Never	136	10.9	Ref.	9.9	Ref.	15.6	Ref.
1-6 days	131	24.2	2.12 (1.11 to 4.02)	11.3	1.13 (0.55 to 2.32)	18.2	0.94 (0.53 to 1.69)
7 days or more	105	33.3	3.67 (1.97 to 6.86)	19.4	2.58 (1.29 to 5.15)	26.2	1.65 (0.92 to 2.96)
Hospitalized for COVID-19							
No	341	19.9	Ref.	12.7	Ref.	18.3	Ref.
Yes	32	48.1	2.72 (1.67 to 4.44)	17.2	1.74 (0.85 to 3.57)	32.0	2.05 (0.97 to 4.32)
COVID-19 symptom severity							
Lowest tertile	115	5.8	Ref.	4.9	Ref.	9.6	Ref.
Mid tertile	161	18.8	2.70 (1.16 to 6.28)	12.1	2.15 (0.81 to 5.70)	20.1	1.76 (0.88 to 3.55)
Highest tertile	97	47.1	6.42 (2.77 to 14.87)	23.9	3.91 (1.45 to 10.51)	30.7	2.70 (1.30 to 5.59)

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

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Flu-like symptoms and mental morbidities

In Figure 1, we present the proportions of individuals with flu-like symptoms lasting at least one week during the preceding two months among recovering COVID-19 patients, those who tested negative and those never tested for SARS-CoV-2 (more detailed in supplementary Table 5).

Individuals who tested negative reported 29-91% higher prevalence of symptoms than those never tested for SARS-CoV-2 (see supplementary Table 6), while individuals with a confirmed COVID-19 diagnosis had, compared to all others, dramatically increased adjusted risk ratios of all symptoms: 3.49 for gastrointestinal symptoms, 3.66 for myalgia, 4.16 for fatigue, 4.58 for sore throat, 4.64 for headache, 9.26 for shortness of breath, 19.10 for fever, and 32.52 for impaired sense of taste or smell (see supplementary Table 7).

We found that flu-like symptom burden was positively associated with symptom levels of depression, anxiety and PTSD, regardless of COVID-19 diagnosis (Figure 2 and supplementary Table 8). A stepwise increase across tertiles in flu-like symptom burden was associated with a rise in mean levels of depression, anxiety and PTSD among patients recovering from COVID-19, individuals who tested negative and those never tested for SARS-CoV-2. Recovering COVID-19 patients reporting low to medium flu-like symptom burden (low and mid tertiles) presented with lower levels of depression and anxiety compared to those with same levels of flu-like symptom burden but without a diagnosis of COVID-19 (Figure 2 and supplementary Table 8).

Finally, when flu-like symptom burden was added to the multivariable models (presented in Table 2), the direction of the adjusted relative risks of depression (0.63, 95% CI 0.51 to 0.77) and PTSD (0.73, 95% CI, 0.57 to 0.93) reversed in patients recovering from COVID-19 compared to others, indicating that flu-like symptoms mediated the risks of mental morbidity in this otherwise pre-pandemic healthy population.

DISCUSSION

The findings of this study suggest that patients recovering from COVID-19 may experience elevated risks of depression and PTSD, particularly if recovering from a severe disease. We found that mental morbidities among recovering COVID-19 patients were strongly associated with older age, greater flu-like symptom burden, extended time confined to bed and hospitalization due to COVID-19.

To our knowledge, this is the first study addressing mental morbidities among recovering COVID-19 patients in a general population setting, including outpatients. Our findings are in line with the vast literature reporting high rates of mental morbidities among current or discharged COVID-19 inpatients.[9, 10, 12, 13] Several mechanisms may play a role in the increased risk of mental health morbidities among patients recovering from a severe COVID-19 illness. These include worries and fear of infecting others, shame or stigma associated with being infected with COVID-19,[29] and uncertainty of the prognosis.[30] Indeed, the diagnosis of potentially life-threatening diseases, e.g. cancer, has previously been associated with a dramatic rise in risks of psychiatric disorders[31] and suicide.[32] In addition, dysregulated immune response, e.g. the documented cytokine storm associated with COVID-19,[33] may independently affect risks of psychiatric disorders in COVID-19 patients,[34] as has been documented in patients with other infections.[35]

Our mediation analysis suggests that flu-like symptom burden mediated the risk elevations in psychiatric morbidities among patients recovering from COVID-19. Moreover, flu-like symptoms among individuals without a confirmed COVID-19 diagnosis were also strongly associated with symptoms of mental morbidities, suggesting that the association is not limited to COVID-19. Indeed, COVID-19 patients reporting low-medium flu-like symptom burden, had lower levels of depression and anxiety than individuals without a diagnosis of COVID-19 but with similar levels of flu-like symptoms. While the healthy pre-pandemic profile of the COVID-19 population may be an indicator of psychological resilience during recovery from COVID-19, it is also possible that the systematic,

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daily surveillance calls to all COVID-19 patients from the specialized COVID-19 outpatient clinic at the National University Hospital had a positive mental health impact on patients.

This population-based study includes more than 20% of all patients diagnosed with COVID-19 by RT-PCR during the first wave of the epidemic in Iceland. The diagnostic rate in Iceland was among the highest worldwide during the first wave of the epidemic,[36, 37] allowing us to perform sensitivity analyses limited to individuals who all had been screened for SARS-CoV-2. The extensive and well-piloted questionnaire allowed us to obtain validated symptom assessment of mental morbidities along with detailed information on flu-like symptom burden for all individuals during the flu season in Iceland, together with a wide range of potential confounders in the association between COVID-19 and mental morbidities.

However, our study is cross-sectional and therefore less informative on the directionality of the studied associations. Indeed, a newly published study using data from the UK Biobank suggests that individuals with a history of pre-pandemic psychiatric disorders are more likely to be hospitalized and die from COVID-19.[38] Thus, it is possible that patients who were already experiencing psychological symptoms suffered the most severe COVID-19-related symptomology yielding the observed associations. However, we included previous diagnoses of psychiatric disorders in all our models which should, to some extent, alleviate this concern. Nevertheless, it is possible that individuals with severe symptoms of depression and anxiety were more likely to report high levels of flu-like symptoms during the preceding two months when responding to the questionnaire, yielding a detrimental outcome-dependent misclassification. Indeed, the instrument to assess flu-like symptom burden included similar items (e.g. fatigue) as are included in the PHQ-9 instrument which, to some extent, could explain the association between COVID-19 and depression.

Yet, more objective assessments of illness severity, e.g. the number of days confined to bed or hospitalized due to COVID-19 -- both of which were strongly associated with mental morbidities among patients -- might to a lesser extent be influenced by the participants' mental status.

Participants recovering from COVID-19 may differ in terms of their mental health status from COVID-19 patients who did not participate in our study. While we were not able to disentangle the direction of such selection, our observed prevalence of depression and anxiety among recovering COVID-19 patients resembles prevalence rates recently reported in a meta-analysis of diverse COVID-19 patient populations elsewhere.[9] Finally, our study is nested within a small, economically and socially secure society with virtually free and high-quality health care for all, thus the findings may not be generalizable to other settings.

In conclusion, the relatively healthy first-wave COVID-19 population in Iceland presented with increased risk of depression and PTSD in the early weeks of recovery from their illness, particularly those recovering from a severe disease. These findings motivate further follow-up studies of mental health among patients recovering from COVID-19 and other serious infections, and heightened clinical surveillance of those recovering from a severe illness.

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Contributors: UAV, TA, and JJ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. UAV, AH, KSS, IM, JJ, TA conceived and design the study. UAV, AH, KSS, IM, JJ, TA analysed the data, and all authors interpreted the data. UAV, KSS, HYH, IM drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. UAV, AH, HR, GT, TA, JJ, SYK, PL, SHE, DGG, ADM provided administrative, technical, or material support. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work (except those described above); no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the National Bioethics Committee of Iceland, Reykjavik (NBC no. 20-073) and the Data Protection Authority.

Data sharing: The original data and R codes are available on request upon approval of the National Bioethics Committee and the Data Protection Authority.

The lead author/guarantor of the study (UAV) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure legends

Figure 1: The proportion of individuals with and without (tested and not tested) a confirmed diagnosis of COVID-19 with flu-like symptoms of one week or more during the last two months before responding to the baseline questionnaire.

Figure 2: Adjusted symptom scores of depression, anxiety and PTSD by flu-like symptom burden among individuals with a recent COVID-19 diagnosis, those who tested negative and those never tested for SARS-CoV-2.

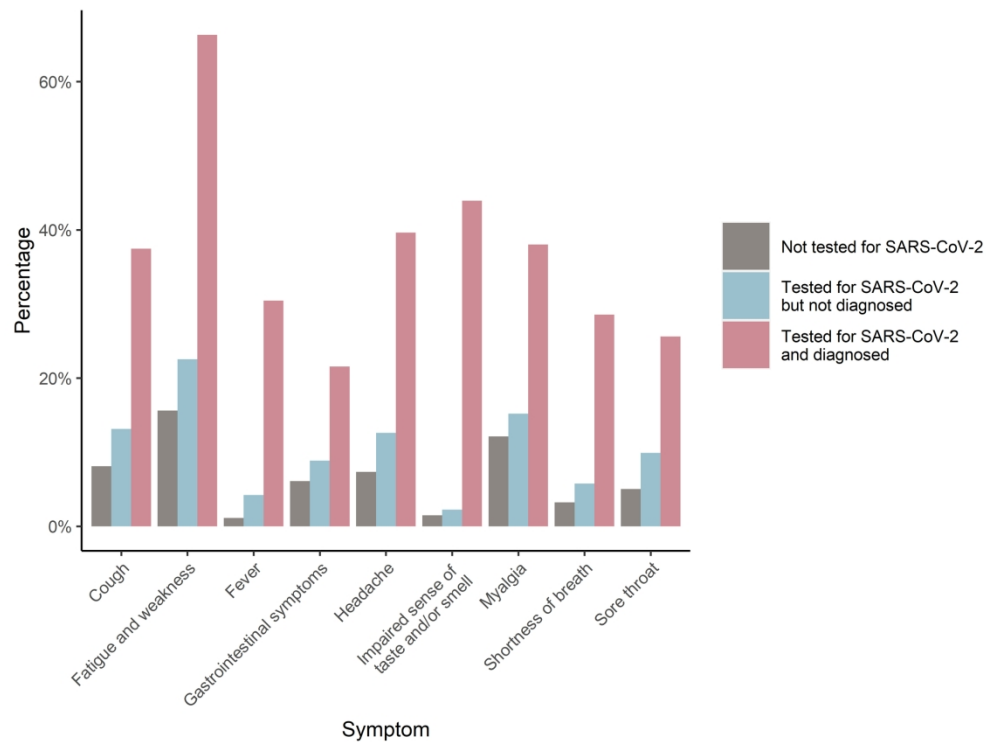


Figure 1 / The proportion of individuals with and without (tested and not tested) a confirmed diagnosis of COVID-19 with flu-like symptoms of one week or more during the last two months before responding to the baseline questionnaire.

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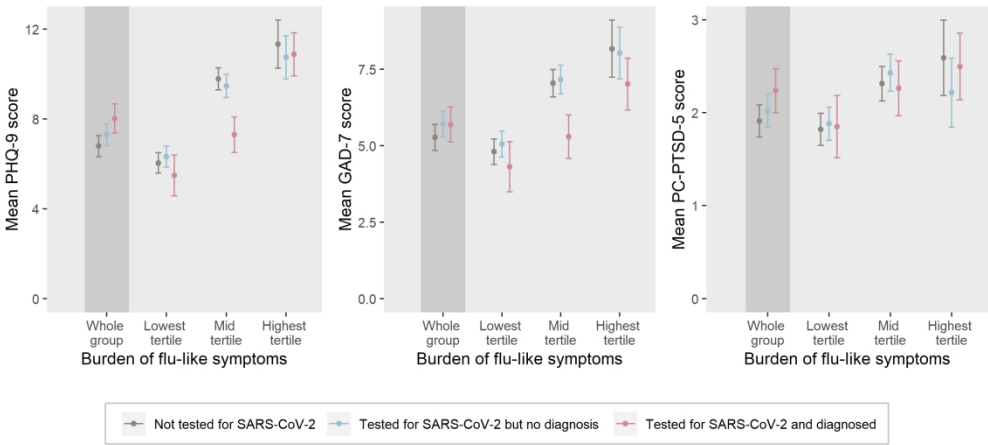
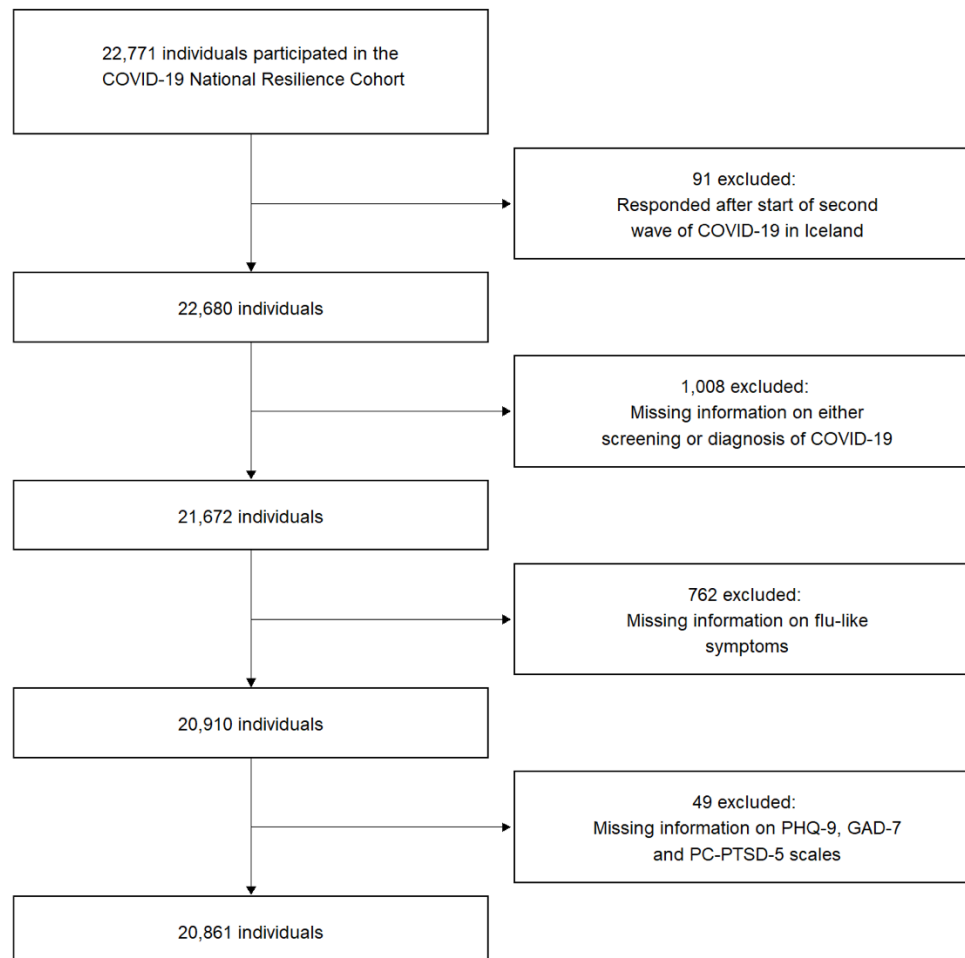


Figure 2 / Adjusted symptom scores of depression, anxiety and PTSD by flu-like symptom burden among individuals with a recent COVID-19 diagnosis, those who tested negative and those never tested for SARS-CoV-2.

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Supplementary material

Supplementary Figure 1. The analytic sample within the COVID-19 National Resilience Cohort.



Supplementary Table 1. Mean and median scores on PHQ-9, GAD-7, and PC-PTSD-5 among individuals with and without a recent COVID-19 diagnosis.

	Mean scores		Median scores		P-value	Adj. P-value
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19		
Depression	5.07	6.11	4	5	<.001	<.001
Anxiety	4.12	4.52	3	4	.07	.08
PTSD	1.72	1.90	2	2	.007	<.001

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 2. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19 (*diagnosed at least two weeks before responding*).

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference	
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19			Crude	Absolute difference % Adjusted ^a %
Depression	2992 (16.2)	73 (22.0)	1.36 (1.11 to 1.67)	1.49 (1.20 to 1.84)	5.8	8.6
Female	2421 (18.8)	55 (24.9)	1.32 (1.05 to 1.67)	1.45 (1.14 to 1.83)	6.1	8.4
Male	559 (10.0)	16 (14.7)	1.47 (0.93 to 2.33)	1.52 (0.93 to 2.49)	4.7	6.9
18-39 years	954 (33.3)	22 (26.8)	0.81 (0.56 to 1.16)	0.95 (0.65 to 1.39)	-6.5	-1.5
40-59 years	1367 (16.8)	39 (22.3)	1.32 (1.00 to 1.75)	1.72 (1.30 to 2.28)	5.5	14.7
≥60 years	671 (8.9)	12 (16.0)	1.79 (1.06 to 3.02)	2.59 (1.53 to 4.39)	7.1	22.0
Anxiety	2120 (11.3)	45 (13.1)	1.16 (0.88 to 1.54)	1.25 (0.94 to 1.67)	1.8	2.9
Female	1759 (13.4)	33 (14.7)	1.10 (0.80 to 1.51)	1.17 (0.84 to 1.64)	1.3	2.3
Male	353 (6.2)	10 (9.1)	1.46 (0.80 to 2.67)	1.46 (0.80 to 2.64)	2.9	3.5
18-39 years	770 (26.2)	13 (15.5)	0.59 (0.36 to 0.98)	0.64 (0.38 to 1.09)	-10.7	-8.6
40-59 years	951 (11.5)	26 (14.4)	1.26 (0.88 to 1.80)	1.68 (1.18 to 2.41)	2.9	10.2
≥60 years	399 (5.2)	5 (6.9)	1.32 (0.57 to 3.10)	2.15 (0.91 to 5.03)	1.7	7.5
PTSD	2699 (15.6)	56 (18.9)	1.21 (0.95 to 1.54)	1.35 (1.06 to 1.73)	3.3	6.7
Female	2198 (18.6)	43 (21.7)	1.17 (0.89 to 1.53)	1.27 (0.97 to 1.67)	3.1	5.7
Male	493 (9.1)	12 (12.4)	1.36 (0.79 to 2.32)	1.64 (0.95 to 2.83)	3.3	7.5
18-39 years	597 (24.2)	10 (14.3)	0.59 (0.33 to 1.05)	0.72 (0.41 to 1.28)	-9.9	-7.4
40-59 years	1268 (16.7)	29 (18.5)	1.11 (0.79 to 1.54)	1.31 (0.94 to 1.84)	1.8	6.7
≥60 years	834 (11.6)	17 (24.6)	2.12 (1.40 to 3.23)	2.70 (1.80 to 4.05)	13.0	28.3

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 3. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19 (*using multiple imputation*).

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference	
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19			Crude	% Adjusted ^a %
Depression	3487 (17.0)	83 (22.3)	1.31 (1.08 to 1.59)	1.44 (1.18 to 1.75)	5.3	8.1
Female	2819 (19.7)	64 (25.6)	1.29 (1.05 to 1.61)	1.43 (1.14 to 1.78)	5.9	8.3
Male	655 (10.7)	17 (14.1)	1.32 (0.85 to 2.08)	1.35 (0.85 to 2.16)	3.4	4.6
18-39 years	1105 (35.2)	26 (28.9)	0.82 (0.59 to 1.14)	0.95 (0.67 to 1.33)	-6.3	-1.8
40-59 years	1565 (17.5)	445(22.5)	1.29 (0.99 to 1.68)	1.68 (1.29 to 2.18)	5.0	14.8
≥60 years	817 (9.7)	12 (14.8)	1.52 (0.90 to 2.58)	2.23 (1.31 to 3.78)	5.1	17.2
Anxiety	2328 (11.3)	45 (12.1)	1.06 (0.81 to 1.40)	1.15 (0.87 to 1.53)	0.8	1.8
Female	1940 (13.5)	34 (13.6)	1.01 (0.73 to 1.38)	1.08 (0.78 to 1.50)	0.1	1.0
Male	378 (6.2)	10 (8.3)	1.34 (0.73 to 2.45)	1.34 (0.74 to 2.43)	2.1	2.6
18-39 years	830 (26.5)	13 (14.4)	0.55 (0.33 to 0.91)	0.61 (0.36 to 1.03)	-12.1	-10.0
40-59 years	1037 (11.6)	27 (13.6)	1.18 (0.83 to 1.68)	1.57 (1.11 to 2.23)	2.0	9.0
≥60 years	461 (5.5)	5 (5.9)	1.08 (0.46 to 2.53)	1.69 (0.72 to 3.97)	0.4	4.6
PTSD	2915 (15.8)	62 (19.2)	1.22 (0.97 to 1.53)	1.36 (1.08 to 1.71)	3.4	6.7
Female	2375 (18.7)	48 (22.1)	1.18 (0.92 to 1.52)	1.29 (1.00 to 1.66)	3.4	6.1
Male	532 (9.2)	13 (12.4)	1.34 (0.80 to 2.25)	1.57 (0.93 to 2.67)	3.2	6.9
18-39 years	642 (24.5)	11 (14.9)	0.61 (0.35 to 1.05)	0.71 (0.41 to 1.22)	-9.6	-7.9
40-59 years	1360 (16.8)	33 (19.3)	1.15 (0.84 to 1.57)	1.37 (1.00 to 1.87)	2.5	7.9
≥60 years	913 (11.8)	18 (23.1)	1.96 (1.30 to 2.96)	2.47 (1.65 to 3.69)	11.3	23.9

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 4. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19 (*analysis limited to individuals who were tested for COVID-19*).

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference	
	Individuals that have been tested for COVID-19 but not diagnosed	Individuals that have been tested for COVID-19 and diagnosed			Crude %	Adjusted ^a %
Depression	885 (19.4)	75 (22.1)	1.14 (0.92 to 1.40)	1.31 (1.06 to 1.62)	2.7	6.1
Female	712 (21.7)	56 (24.8)	1.14 (0.90 to 1.45)	1.30 (1.02 to 1.65)	3.1	6.2
Male	168 (13.2)	17 (15.2)	1.15 (0.72 to 1.82)	1.22 (0.75 to 1.97)	2.0	3.7
18-39 years	275 (37.6)	23 (27.1)	0.72 (0.50 to 1.03)	0.85 (0.58 to 1.23)	-10.5	-5.2
40-59 years	413 (17.8)	40 (22.3)	1.26 (0.94 to 1.68)	1.64 (1.23 to 2.17)	4.5	13.6
≥60 years	197 (13.1)	12 (15.8)	1.21 (0.71 to 2.07)	1.86 (1.09 to 3.18)	2.7	16.4
Anxiety	640 (13.8)	45 (13.1)	0.95 (0.72 to 1.26)	1.08 (0.81 to 1.44)	-0.7	1.1
Female	531 (15.9)	34 (14.8)	0.94 (0.68 to 1.29)	1.04 (0.75 to 1.45)	-1.1	0.6
Male	106 (8.2)	10 (8.9)	1.08 (0.58 to 2.01)	1.11 (0.60 to 2.04)	0.7	1.0
18-39 years	237 (31.3)	13 (14.9)	0.48 (0.29 to 0.80)	0.52 (0.31 to 0.89)	-16.4	-13.4
40-59 years	286 (12.1)	27 (14.7)	1.21 (0.84 to 1.75)	1.62 (1.13 to 2.31)	2.6	9.7
≥60 years	117 (7.7)	5 (6.9)	0.90 (0.38 to 2.12)	1.56 (0.66 to 3.70)	-0.8	5.1
PTSD	747 (17.8)	59 (19.5)	1.09 (0.86 to 1.39)	1.26 (0.99 to 1.60)	1.7	5.4
Female	626 (21.1)	46 (22.7)	1.08 (0.83 to 1.40)	1.19 (0.91 to 1.56)	1.6	4.5
Male	119 (9.7)	12 (12.1)	1.25 (0.71 to 2.17)	1.52 (0.86 to 2.67)	2.4	6.5
18-39 years	168 (27.6)	11 (15.3)	0.55 (0.32 to 0.97)	0.68 (0.39 to 1.18)	-12.3	-9.6
40-59 years	376 (17.4)	31 (19.3)	1.11 (0.80 to 1.54)	1.31 (0.94 to 1.83)	1.9	6.9
≥60 years	203 (14.2)	17 (24.3)	1.70 (1.11 to 2.63)	2.22 (1.46 to 3.37)	10.1	24.6

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 5. Raw prevalence of flu-like symptoms during the preceding two months among individuals with and without a recent COVID-19 diagnosis.

	No. (%)		P-value
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)	
No reported symptoms			
Yes	3023 (14.8)	12 (3.2)	<.001
No	17465 (85.2)	361 (96.8)	
Cough			
Never	13181 (64.3)	122 (32.7)	<.001
1-2 days	3658 (17.9)	57 (15.3)	
3-6 days	1734 (8.5)	55 (14.7)	
1-2 weeks	754 (3.7)	54 (14.5)	
Over 2 weeks	1161 (5.7)	85 (22.8)	
Fatigue and weakness			
Never	7535 (36.8)	32 (8.6)	<.001
1-2 days	6044 (29.5)	39 (10.5)	
3-6 days	3350 (16.4)	54 (14.5)	
1-2 weeks	1276 (6.2)	59 (15.8)	
Over 2 weeks	2283 (11.1)	189 (50.7)	
Fever			
Never	17362 (84.7)	127 (34.0)	<.001
1-2 days	1907 (9.3)	58 (15.5)	
3-6 days	831 (4.1)	74 (19.8)	
1-2 weeks	227 (1.1)	53 (14.2)	
Over 2 weeks	161 (0.8)	61 (16.4)	
Gastrointestinal symptoms			
Never	12589 (61.4)	162 (43.4)	<.001
1-2 days	4565 (22.3)	69 (18.5)	
3-6 days	1941 (9.5)	61 (16.4)	
1-2 weeks	585 (2.9)	42 (11.3)	
Over 2 weeks	808 (3.9)	39 (10.5)	
Headache			
Never	8583 (41.9)	73 (19.6)	<.001
1-2 days	6754 (33.0)	57 (15.3)	
3-6 days	3381 (16.5)	95 (25.5)	
1-2 weeks	816 (4.0)	62 (16.6)	
Over 2 weeks	954 (4.7)	86 (23.1)	

	No. (%)		P- value
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)	
Impaired sense of taste and/or smell			
Never	19514 (95.2)	140 (37.5)	<.001
1-2 days	411 (2.0)	25 (6.7)	
3-6 days	220 (1.1)	44 (11.8)	
1-2 weeks	111 (0.5)	55 (14.7)	
Over 2 weeks	232 (1.1)	109 (29.2)	
Myalgia			
Never	12253 (59.8)	105 (28.2)	<.001
1-2 days	3512 (17.1)	54 (14.5)	
3-6 days	2072 (10.1)	72 (19.3)	
1-2 weeks	708 (3.5)	81 (21.7)	
Over 2 weeks	1943 (9.5)	61 (16.4)	
Shortness of breath			
Never	17111 (83.5)	169 (45.3)	<.001
1-2 days	1809 (8.8)	42 (11.3)	
3-6 days	775 (3.8)	55 (14.7)	
1-2 weeks	312 (1.5)	41 (11.0)	
Over 2 weeks	481 (2.3)	66 (17.7)	
Sore throat			
Never	12987 (63.4)	153 (41.0)	<.001
1-2 days	4323 (21.1)	62 (16.6)	
3-6 days	1901 (9.3)	63 (16.9)	
1-2 weeks	632 (3.1)	39 (10.5)	
Over 2 weeks	645 (3.1)	56 (15.0)	

Supplementary Table 6. Prevalence, crude and adjusted relative risks with 95% confidence intervals of flu-like symptoms lasting for 1 week or more, during the preceding two months, among individuals who tested negative for SARS-CoV-2 and those who were never tested.

Symptoms	No. (%)		cRR (95% CI)	aRR (95% CI) ^a
	Individuals not tested for SARS-CoV-2 (n = 15442)	Individuals tested negative for SARS-CoV-2 (n = 5046)		
Cough	1249 (8.1)	666 (13.2)	1.60 (1.46 to 1.76)	1.59 (1.45 to 1.75)
Fatigue and weakness	2420 (15.7)	1139 (22.3)	1.45 (1.36 to 1.55)	1.37 (1.29 to 1.46)
Fever	176 (1.1)	212 (4.2)	3.71 (3.02 to 4.56)	3.49 (2.84 to 4.29)
Gastrointestinal symptoms	946 (6.1)	447 (8.9)	1.48 (1.33 to 1.66)	1.37 (1.23 to 1.53)
Headache	1134 (7.3)	636 (12.6)	1.74 (1.58 to 1.91)	1.60 (1.46 to 1.75)
Impaired sense of taste or smell	229 (1.5)	114 (2.3)	1.53 (1.21 to 1.93)	1.64 (1.30 to 2.07)
Myalgia	1881 (12.2)	770 (15.3)	1.26 (1.16 to 1.36)	1.29 (1.19 to 1.39)
Shortness of breath	503 (3.3)	290 (5.7)	1.88 (1.62 to 2.17)	1.84 (1.59 to 2.13)
Sore throat	778 (5.0)	499 (9.9)	1.98 (1.77 to 2.21)	1.91 (1.71 to 2.14)

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 7. Prevalence, crude and adjusted relative risks with 95% confidence intervals of flu-like symptoms lasting for 1 week or more, during the preceding two months, among individuals with and without a confirmed diagnosis of COVID-19.

Symptoms	No. (%)		cRR (95% CI)	aRR (95% CI) ^a
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)		
Cough	1915 (9.4)	139 (37.3)	4.15 (3.60 to 4.76)	5.02 (4.35 to 5.81)
Fatigue and weakness	3559 (17.4)	248 (66.5)	3.93 (3.63 to 4.26)	4.16 (3.77 to 4.60)
Fever	388 (1.9)	114 (30.6)	16.77 (13.93 to 20.19)	19.10 (15.49 to 23.48)
Gastrointestinal symptoms	1393 (6.8)	81 (21.7)	3.29 (2.69 to 4.06)	3.49 (2.82 to 4.32)
Headache	1770 (8.6)	148 (39.7)	4.67 (4.10 to 5.37)	4.64 (3.99 to 5.39)
Impaired sense of taste or smell	343 (1.7)	164 (44.0)	27.04 (23.10 to 31.82)	32.52 (27.22 to 38.86)
Myalgia	2651 (12.9)	142 (38.1)	3.03 (2.65 to 3.49)	3.66 (3.16 to 4.23)
Shortness of breath	793 (3.9)	107 (28.7)	7.53 (6.05 to 9.03)	9.26 (7.61 to 11.25)
Sore throat	1277 (6.2)	95 (25.5)	4.17 (3.46 to 5.00)	4.58 (3.78 to 5.54)

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 8. Adjusted mean symptom scores of depression, anxiety and PTSD by flu-like symptom burden in tertiles among individuals with a recent COVID-19 diagnosis, those who tested negative and those never tested for SARS-CoV-2.

	Multivariable adjusted mean value by tertile of flu-like symptoms ^a			Beta (95% CI)	P-value
	Lowest tertile	Mid tertile	Highest tertile		
Depression					
Patients with COVID-19	5.49	7.30	10.89	0.24 (0.17 to 0.30)	<.001
Tested negative for SARS-CoV-2	6.33	9.48	10.75	0.29 (0.25 to 0.33)	<.001
Not tested for SARS-CoV-2	6.04	9.79	11.34	0.34 (0.33 to 0.36)	<.001
Anxiety					
Patients with COVID-19	4.31	5.29	7.02	0.12 (0.06 to 0.17)	<.001
Tested negative for SARS-CoV-2	5.06	7.16	8.02	0.19 (0.16 to 0.23)	.03
Not tested for SARS-CoV-2	4.81	7.04	8.17	0.22 (0.20 to 0.23)	<.001
PTSD					
Patients with COVID-19	1.85	2.26	2.50	0.03 (0.01 to 0.05)	<.001
Tested negative for SARS-CoV-2	1.88	2.43	2.21	0.05 (0.04 to 0.06)	.02
Not tested for SARS-CoV-2	1.82	2.31	2.59	0.06 (0.06 to 0.07)	<.001

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectional reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	#4	Present key elements of study design early in the paper	7

1	Setting	#5	Describe the setting, locations, and relevant dates,	7
2			including periods of recruitment, exposure, follow-up,	
3			and data collection	
4				
5				
6	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods	7
7			of selection of participants.	
8				
9				
10		#7	Clearly define all outcomes, exposures, predictors,	8-9
11			potential confounders, and effect modifiers. Give	
12			diagnostic criteria, if applicable	
13				
14				
15	Data sources /	#8	For each variable of interest give sources of data and	8-9
16	measurement		details of methods of assessment (measurement).	
17			Describe comparability of assessment methods if there is	
18			more than one group. Give information separately for for	
19			exposed and unexposed groups if applicable.	
20				
21				
22				
23	Bias	#9	Describe any efforts to address potential sources of bias	19-20
24				
25				
26	Study size	#10	Explain how the study size was arrived at	7
27				
28	Quantitative	#11	Explain how quantitative variables were handled in the	8-9
29	variables		analyses. If applicable, describe which groupings were	
30			chosen, and why	
31				
32				
33	Statistical	#12a	Describe all statistical methods, including those used to	9-11
34	methods		control for confounding	
35				
36				
37	Statistical	#12b	Describe any methods used to examine subgroups and	10-11
38	methods		interactions	
39				
40				
41	Statistical	#12c	Explain how missing data were addressed	10
42	methods			
43				
44				
45	Statistical	#12d	If applicable, describe analytical methods taking account	n/a
46	methods		of sampling strategy	
47				
48				
49	Statistical	#12e	Describe any sensitivity analyses	10
50	methods			
51				
52				
53	Results			
54				
55	Participants	#13a	Report numbers of individuals at each stage of study—eg	11-12
56			numbers potentially eligible, examined for eligibility,	
57			confirmed eligible, included in the study, completing	
58				
59				
60				

follow-up, and analysed. Give information separately for
for exposed and unexposed groups if applicable.

Participants	#13b	Give reasons for non-participation at each stage	7 (addressed in the methods chapter)
Participants	#13c	Consider use of a flow diagram	Supplementary material: page 1, Supplementary Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	11-13
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	7 (addressed in the methods chapter)
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	14-17
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
Main results	#16b	Report category boundaries when continuous variables were categorized	9 (addressed in the methods chapter)
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14-16
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	#18	Summarise key results with reference to study objectives	18
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19-20

1	Interpretation	#20	Give a cautious overall interpretation considering	18-20
2			objectives, limitations, multiplicity of analyses, results	
3			from similar studies, and other relevant evidence.	
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6	Generalisability	#21	Discuss the generalisability (external validity) of the	20
7			study results	
8				
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10	Other			
11	Information			
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13				
14	Funding	#22	Give the source of funding and the role of the funders for	21
15			the present study and, if applicable, for the original study	
16			on which the present article is based	
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18				

Notes:

- 13b: 7 (addressed in the methods chapter)
- 13c: Supplementary material: page 1, Supplementary Figure 1
- 14b: 7 (addressed in the methods chapter)
- 16b: 9 (addressed in the methods chapter)

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BMJ Open

Illness severity and risk of mental morbidities among patients recovering from COVID-19: a cross-sectional study in the Icelandic population

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**Illness severity and risk of mental morbidities among patients recovering from COVID-19:
a cross-sectional study in the Icelandic population**

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Abstract

Objective

To test if patients recovering from COVID-19 are at increased risk of mental morbidities and to what extent such risk is exacerbated by illness severity.

Design

Population-based cross-sectional study.

Setting

Iceland.

Participants

A total of 22,861 individuals were recruited through invitations to existing nationwide cohorts and a social media campaign from April 24 to July 22 2020, of which 373 were patients recovering from COVID-19.

Main outcome measures

Symptoms of depression (Patient Health Questionnaire [PHQ-9]), anxiety (General Anxiety Disorder Scale [GAD-7]), and PTSD (modified Primary Care PTSD Screen for DSM-5 [PC-PTSD-5]) above screening thresholds. Adjusting for multiple covariates and comorbidities, multivariable Poisson regression was used to assess the association between COVID-19 severity and mental morbidities.

Results

Compared to individuals without a diagnosis of COVID-19, patients recovering from COVID-19 had increased risk of depression (22.1% vs. 16.2%; aRR 1.48, 95% CI 1.20 to 1.82) and PTSD (19.5% vs.

15.6%; aRR 1.38, 95% CI 1.09 to 1.75) but not anxiety (13.1% vs. 11.3%; aRR 1.24, 95% CI 0.93 to 1.64). Elevated relative risks were limited to recovering COVID-19 patients 40 years or older and were particularly high among individuals with university education. Among recovering COVID-19 patients, symptoms of depression were particularly common among those in the highest, compared to the lowest tertile of flu-like symptom burden (47.1% vs. 5.8%; aRR 6.42, 95% CI 2.77 to 14.87), among patients confined to bed for seven days or longer compared to those never confined to bed (33.3% vs. 10.9%; aRR 3.67, 95% CI 1.97 to 6.86), and among patients hospitalized for COVID-19 compared to those never admitted to hospital (48.1% vs. 19.9%; aRR 2.72, 95% CI 1.67 to 4.44).

Conclusions

Severe disease course is associated with increased risk of depression and PTSD among patients recovering from COVID-19.

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Strengths and limitations of this study

- To our knowledge, this is the first study addressing mental morbidities among recovering COVID-19 patients in a general population setting, including outpatients.
- This study includes more than 20% of all patients diagnosed with COVID-19 by RT-PCR during the first wave of the epidemic in Iceland, where the diagnostic rate was among the highest worldwide, allowing us to perform sensitivity analyses limited to individuals who all had been screened for SARS-CoV-2.
- The extensive and well-piloted questionnaire allowed us to obtain validated symptom assessment of mental morbidities along with detailed information on flu-like symptom burden for all individuals during the flu season in Iceland.
- The cross-sectional design is less informative on the directionality of the studied associations, and as the study is nested within a small, economically and socially secure society, the generalizability of the findings may be limited.
- It is possible that individuals with severe symptoms of depression and anxiety were more likely to report high levels of flu-like symptoms during the preceding two months when responding to the questionnaire, yielding a outcome-dependent misclassification.

INTRODUCTION

With almost 180 million reported cases and 3.9 million deaths globally,[1] the coronavirus disease 2019 (COVID-19) pandemic remains a major public health challenge worldwide. Beyond the extensive socioeconomic impact and suffering of patients during the illness, there are rising concerns about long-term somatic and psychological impact on recovering patients.[2-6]

Mental health consequences among patients in recent epidemics are well documented.[7, 8] With respect to COVID-19, a meta-analysis of 31 studies suggested a 45-47% pooled prevalence of mild to severe symptoms of depression and anxiety in patients with COVID-19, mostly inpatients.[9] Moreover, extreme rates of posttraumatic stress have been reported among COVID-19 inpatients in China.[10, 11] Previous studies are often small, limited to inpatients, and some lack a control group. Fewer studies have reported symptoms of mental morbidities after recovery from COVID-19 with existing data suggesting high levels of symptoms[12] and elevated rates of diagnosed psychiatric disorders among COVID-19 inpatients during the first weeks and months after hospital discharge.[13-15]

Flu-like symptoms, such as myalgia, cough and sore throat, have been associated with mental morbidities in the general population during the COVID-19 pandemic.[16, 17] To what extent flu-like symptoms are associated with psychological distress in recently recovered COVID-19 patients remains unknown. There are several mechanisms through which COVID-19 may be associated with mental morbidity. Firstly, uncertainty regarding the disease course may give rise to symptoms of anxiety and depression in infected patients.[18] Secondly, serious infection may induce a cytokine storm,[19, 20] leading to exacerbation of the illness and development of psychological symptoms such as depression.[19] The reverse may also be true that psychological symptoms may cause more severe COVID-19 illness through excessive or dysregulated inflammation.[21]

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The first wave of COVID-19 in Iceland started on February 28. Through modest but systematic mitigation strategies[22] the incidence of COVID-19 had effectively been attenuated by the end of April 2020, with only sporadic cases occurring until the onset of the second wave of infections on July 22. During this period, more than 20% of the total population was tested using reverse transcription-polymerase chain reaction (RT-PCR); a total of 1820 tested positive for SARS-CoV-2 (0.5% of the total population), of whom 113 were hospitalized (6%), and ten died (0.5%).[23] Here we explore mental health indicators in patients recovering from COVID-19 in the first wave of the pandemic and the potential role of disease severity on the risk of mental morbidities.

METHODS

Study population and design

The COVID-19 National Resilience Cohort was established on April 24, 2020, with the overarching aim of understanding the long-term public health impact of the COVID-19 epidemic in Iceland.[24] Eligible were all Icelandic and English speaking individuals 18 years or older who had an Icelandic electronic ID (total population ≥ 18 years on January 1, 2020 was 282,770[25]). Recruitment was mainly through social media and public media coverage, though participants in ongoing cohort studies (The SAGA cohort [N = 31,795 women]; iStopMM [N = 80,730 men and women], and Health and well-being of Icelanders [N = 6,102 men and women]) received email or postal invitations to participate. In addition, all individuals in Iceland who tested positive by RT-PCR for SARS-CoV-2 through May 2020 (N = 1,800) received a text message invitation, on June 3, 2020. All participants signed an electronic informed consent and subsequently answered a web-based questionnaire. The study was approved by the National Bioethics Committee (NBC no. 20-073) and the Data Protection Authority.

We performed a cross-sectional analysis of participants responding to the baseline questionnaire from April 24 through July 22, 2020. A total of 22,680 individuals had participated at that time point.

We excluded individuals who did not state whether or not they had undergone a diagnostic test (n = 989) or been diagnosed with COVID-19 (n = 19), and those who did not answer all questions on flu-like symptoms (n = 762) or all items in any one of the three measures of depression, anxiety and posttraumatic stress (n = 49) (see supplementary Figure 1). The final analytic sample consisted of 20,861 participants.

Measures

Sociodemographic and health-related factors

Sociodemographic information included the date of response to the baseline questionnaire, gender, age, education, average monthly income during the past year, relationship status, and residency (capital vs. other regions). We defined relationship status as either being in a relationship (married, cohabiting, or in a relationship yet not cohabiting) or not (single, widowed or divorced). Highest level of education was defined as 1) compulsory; 2) upper secondary/vocational/other; 3) university exam (bachelor's degree or diploma certificate); or 4) master's or doctoral degree. Monthly income categories were defined as 1) low income, <1.653 GBP; 2) low-medium income, 1.653-2.755 GBP; 3) medium income, 2.756-3.858 GBP; 4) medium-high income, 3.859-5.511 GBP; 5) high income, >5.511 GBP (conversion rates according to The Central Bank of Iceland, April 24, 2020[26]).

Health-related information included current smoking status (yes/no), binge drinking during the past two months (defined as ≥ 4 drinks for women and ≥ 5 drinks for men or other genders[27]), a previous diagnosis of a psychiatric disorder (made by physicians or psychologists; yes/no), and previous diagnosis of somatic comorbidities including hypertension, diabetes, heart disease, lung disease, chronic kidney disease, cancer, and immunosuppressive state or immunosuppressive therapy (none, one, or two or more comorbid conditions). Additionally, participants reported their height (m) and weight (kg), which was used to estimate body mass index (BMI) as kg/m^2 .

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Diagnosis of COVID-19 and illness severity

We asked participants if they had been tested for COVID-19 regardless of testing method. If they responded yes, we asked if they had been diagnosed with COVID-19, and if so, how long ago they had been diagnosed, how long they were confined to bed due to COVID-19, and whether they had been hospitalized.

As the first wave of COVID-19 coincided with the flu season in Iceland, we asked all participants how many days they had experienced nine specific flu-like symptoms over the preceding two months. The symptoms, previously identified as relevant for COVID-19,[28, 29] were: fever, cough, sore throat, impaired sense of taste or smell, headache, myalgia (body aches), gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), shortness of breath, fatigue and weakness. Response options were: “never”, “1-2 days”, “3-6 days”, “1-2 weeks”, and “more than 2 weeks”, which were scored from “0” (never) to “4” (≥2 weeks). We calculated flu-like symptom burden by summing all symptom scores indicated by each participant (range 0-36 points) and then divided scores into tertiles of the distribution within the COVID-19 cohort (lowest 0-11, mid 12-23, highest 24-36 points).

Symptoms of mental illness

We used the 9-item-Patient Health Questionnaire (PHQ-9) to measure symptoms of depression with the recommended cut-off of ≥10 points serving as a screening indicator for depression in an adult primary care sample.[30] We used the 7-item Generalized Anxiety Disorder scale (GAD-7) to assess symptoms of anxiety. A cut-off of ≥10 was employed as an indicator of moderate to severe symptoms of a generalized anxiety disorder in an adult primary care sample.[31] The 5-item Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) was used to measure symptoms of posttraumatic stress,[32] with a modified version tailored to COVID-19 (*e.g.*, “Had nightmares about COVID-19?”). We scored the responses as “0” (never) or “1” (seldom, sometimes, often, very often) with a total

score ranging from 0-5. We defined COVID-19-specific PTSD as a PC-PTSD-DSM-5 score of ≥ 4 , which has previously been reported as optimal.[32]

Statistical analysis

First, we contrasted the distribution of sociodemographic and health-related factors between individuals with and without a COVID-19 diagnosis. We then ran univariable and multivariable linear regression to detect potential differences in continuous symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) across groups with and without a confirmed COVID-19 diagnosis. We used robust (modified) Poisson regression, with the classical sandwich estimator,[33] to determine the association between a confirmed diagnosis of COVID-19 and risk of depression, anxiety, or PTSD surpassing cut-offs of potential clinical significance. The association is presented as unadjusted and adjusted relative risks (aRRs) with 95% confidence intervals (CIs) and as prevalence differences. All multivariable models included age (continuous), gender (male, female, or other), educational level (classification described above), income (continuous), current smoking (yes/no), previous diagnosis of a psychiatric disorder (yes/no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and the time period of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22). We then performed these analyses stratified by all covariates and performed a likelihood ratio test for effect modification.

We performed several sensitivity analyses. As we were concerned for a potential overlap between physical symptoms of COVID-19 and some items on the mental health assessments (e.g. fatigue), we performed a sensitivity analysis excluding COVID-19 patients diagnosed within 14 days of responding to the questionnaire. We further, reran the analysis using individuals tested but not positive for COVID-19 as a control group. There was a considerable difference between individuals with and without a COVID-19 diagnosis with respect to the date of responding to the questionnaire (Table 1). Therefore, we repeated the multivariable Poisson regression stratified by questionnaire answer

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3 date, divided into two groups (April 24-May 7, and May 8-July 22). Finally, as our primary Poisson
4 regression analysis included individuals with complete responses to PHQ-9 (n = 18,822), GAD-7 (n =
5 19,163) and PC-PTSD-5 (n = 17,562), we repeated these analyses, including the entire analytic
6 sample (n = 20,861), using multiple imputation by creating 10 imputed data sets with 10 iterations
7 each.[34]
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16 Limited to individuals diagnosed with COVID-19, we used multivariable Poisson regression to
17 evaluate the association between indicators of COVID-19 severity and mental morbidities. Adjusting
18 for the same covariates as listed above, we explored the association between time confined to bed
19 due to COVID-19 (never vs. 1-6 days or 7 days or more), flu-like symptom burden (in tertiles) and
20 whether or not patients had been hospitalized, and mental morbidities among recovering patients.
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30 Next we compared the proportion of individuals with and without COVID-19 (tested and not tested
31 for SARS-CoV-2) who reported each of nine flu-like symptoms for one week or more. We used robust
32 Poisson regression to calculate unadjusted and multivariable-adjusted relative risks of each
33 symptom among individuals tested vs. not tested for SARS-CoV-2, and then diagnosed vs. not
34 diagnosed with COVID-19. The multivariable models included the same covariates as listed above.
35
36 Using linear regression, we then tested the association between flu-like symptom burden and
37 mental morbidities both among individuals with and without a diagnosis of COVID-19 (tested and
38 not tested for SARS-CoV-2). We then tested whether flu-like symptoms mediated the association
39 between a confirmed COVID-19 diagnosis and mental morbidities by adding flu-like symptoms to the
40 multivariable models. All analyses were conducted in R (Version 3.6.2)
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54 **Patient and public involvement**

55 No patients were involved in putting forward the research question or the outcome measures, nor
56 were they involved in developing plans for design or implementation of the study. Dissemination of
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the results to study participants and the Icelandic population will be obtained through a media outreach (e.g., press release and communication on our study website) on publication of this study.

RESULTS

Background characteristics

Of the 20,861 participants, 5,419 individuals had been tested for SARS-CoV-2, of whom 373 reported having been diagnosed with COVID-19 (97.9% more than two weeks before responding to the questionnaire; Table 1). Compared to other participants, individuals previously diagnosed with COVID-19 were younger (mean age: 48.3 vs. 54.8 years), had a higher educational level and income and were more likely to binge drink alcohol. They were furthermore less likely to be current smokers and have previously been diagnosed with psychiatric disorders or somatic diseases. The analytic sample had similar education[35] and residence distribution as the general population, while the median age was higher and women were overrepresented.[36]

Table 1: Characteristics of the study population, with and without a diagnosis of COVID-19.

	No. (%)		P-value
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)	
Gender			
Male	6133 (29.9)	121 (32.4)	.15
Female	14306 (69.8)	250 (67.0)	
Other	36 (0.2)	2 (0.5)	
Missing	13 (0.1)	0 (0)	
Age			
18-29 years	1191 (5.8)	51 (13.7)	<.001
30-39 years	1949 (9.5)	39 (10.5)	
40-49 years	3644 (17.8)	99 (26.5)	
50-59 years	5309 (25.9)	99 (26.5)	
60-69 years	5359 (26.2)	74 (19.8)	
70 years or older	3036 (14.8)	11 (2.9)	

Highest educational level

Compulsory education	2865 (14.0)	30 (8.0)	.008
Upper secondary, vocational or other education	6303 (30.8)	117 (31.4)	
Bachelor's degree or diploma certificate	6517 (31.8)	135 (36.2)	
Master's or Ph.D. degree	4685 (22.9)	91 (24.4)	
Missing	118 (0.6)	0 (0)	

Average monthly income^a

Low income	3527 (17.2)	50 (13.4)	<.001
Low-medium income	5642 (27.5)	88 (23.6)	
Medium income	4993 (24.4)	82 (22.0)	
Medium-high income	3527 (17.2)	91 (24.4)	
High income	1825 (8.9)	47 (12.6)	
Missing	974 (4.8)	15 (4.0)	

Residence

Capital area	13986 (68.3)	270 (72.4)	.18
Elsewhere in Iceland	6352 (31.0)	102 (27.3)	
Abroad	140 (0.7)	1 (0.3)	
Missing	10 (0.0)	0 (0)	

Marital status

In a relationship	15735 (76.8)	302 (81.0)	.09
Single	4671 (22.8)	71 (19.0)	
Missing	82 (0.4)	0 (0)	

BMI category

< 25, Normal weight	5931 (28.9)	112 (30.0)	.70
25-30, Overweight	7931 (38.7)	138 (37.0)	
> 30, Obese	6127 (29.9)	118 (31.6)	
Missing	499 (2.4)	5 (1.3)	

Smoking status

No	17873 (87.2)	345 (92.5)	.002
Yes	2521 (12.3)	26 (7.0)	
Missing	94 (0.5)	2 (0.5)	

Binge drinking

No	18255 (89.1)	312 (83.6)	.02
Yes	2233 (10.9)	61 (16.4)	

Previous diagnosis of psychiatric disorder

No	14510 (70.8)	285 (76.4)	.02
Yes	5776 (28.2)	84 (22.5)	
Missing	202 (1.0)	4 (1.1)	

Physical diseases

No comorbidities	11958 (58.4)	263 (70.5)	<.001
One comorbidity	5964 (29.1)	86 (23.1)	
2 or more comorbidities	2453 (12.0)	21 (5.6)	
Missing	113 (0.6)	3 (0.8)	
Questionnaire answer date			
April 24-30	7841 (38.3)	102 (27.3)	<.001
May 1-7	5413 (26.4)	76 (20.4)	
May 8-23	4999 (24.4)	53 (14.2)	
May 24-July 22	2235 (10.9)	142 (38.1)	
Time since diagnosis			
Less than 2 weeks	-	8 (2.1)	-
2-4 weeks	-	60 (16.1)	
More than 4 weeks	-	305 (81.8)	

^a Income categories were defined as: Low income, <1.653 GBP; Low-medium income, 1.653-2.755 GBP; Medium income, 2.756-3.858 GBP; Medium-high income, 3.859-5.511 GBP; High income, >5.511 GBP (Conversion rates according to Central Bank of Iceland, April 24, 2020)

COVID-19 and mental morbidities

Individuals diagnosed with COVID-19 reported, compared to others, higher mean scores of depression (6.11 vs. 5.07; $P<.001$) and PTSD (1.90 vs. 1.72; $P<.001$), but not anxiety (4.52 vs. 4.12; $P = 0.08$; see supplementary Table 1). Similarly, multivariable-adjusted relative risks of depression (22.1% vs. 16.2%; aRR 1.48, 95% CI 1.20 to 1.82) and PTSD (19.5% vs. 15.6%; aRR 1.38, 95% CI 1.09 to 1.75) above symptom thresholds were increased among those recovering from COVID-19 compared to others, while not on anxiety (13.1% vs. 11.3%; aRR 1.24, 95% CI 0.93 to 1.64; Table 2). Risk elevations in mental morbidity in COVID-19 patients was limited to those 40 years or older and was highest among individuals 60 years or older (see supplementary Table 2). Individuals with higher educational level were more likely to suffer from symptoms of depression and anxiety after a diagnosis of COVID-19. When stratified by answer date, risk elevations for depression and anxiety in COVID-19 patients were lower for those who answered in the later response period (i.e., May 8-July 22), whereas it was higher for PTSD (see supplementary Table 2) and no statistically significant interactions were observed. Limiting the analysis to individuals who were diagnosed with COVID-19

more than two weeks before responding to the questionnaire and repeating the analysis using multiple imputation, yielded virtually identical results (see supplementary Table 3 and 4, respectively). Finally, limiting the analysis to individuals who were tested for COVID-19 generated a similar pattern yet slightly lower point estimate (see supplementary Table 5).

Table 2: The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19.

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference Crude %	Absolute difference Adjusted ^a %
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID- 19				
Depression	2992 (16.2)	75 (22.1)	1.36 (1.11 to 1.67)	1.48 (1.20 to 1.82)	5.9	8.4
Anxiety	2120 (11.3)	45 (13.1)	1.16 (0.88 to 1.53)	1.24 (0.93 to 1.64)	1.8	2.6
PTSD	2699 (15.6)	59 (19.5)	1.25 (0.99 to 1.57)	1.38 (1.09 to 1.75)	3.9	7.2

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

COVID-19 illness severity and mental morbidities

In Table 3, we show the prevalence and adjusted relative risks of mental morbidities among individuals with a diagnosis of COVID-19 by number of days confined to bed, hospitalization and severity of COVID-19 symptoms. We observed dose-dependent associations between these indices of COVID-19 severity and risk of mental morbidities. Risk elevations by days confined to bed and hospitalization due to COVID-19 were statistically significant for depression and anxiety, while flu-like symptom burden was associated with all measures of psychological morbidity.

Table 3: Prevalence and adjusted relative risks (95% confidence intervals) of mental morbidities among recently recovered patients from COVID-19 by disease and symptom severity.

		Depression		Anxiety		PTSD	
	n	% ≥10 PHQ-9	aRR ^a (95%CI)	% ≥10 GAD-7	aRR ^a (95%CI)	% ≥4 PC- PTSD-5	aRR ^a (95%CI)
Confined to bed due to COVID-19							
Never	136	10.9	Ref.	9.9	Ref.	15.6	Ref.
1-6 days	131	24.2	2.12 (1.11 to 4.02)	11.3	1.13 (0.55 to 2.32)	18.2	0.94 (0.53 to 1.69)
7 days or more	105	33.3	3.67 (1.97 to 6.86)	19.4	2.58 (1.29 to 5.15)	26.2	1.65 (0.92 to 2.96)
Hospitalized for COVID-19							
No	341	19.9	Ref.	12.7	Ref.	18.3	Ref.
Yes	32	48.1	2.72 (1.67 to 4.44)	17.2	1.74 (0.85 to 3.57)	32.0	2.05 (0.97 to 4.32)
COVID-19 symptom severity							
Lowest tertile	115	5.8	Ref.	4.9	Ref.	9.6	Ref.
Mid tertile	161	18.8	2.70 (1.16 to 6.28)	12.1	2.15 (0.81 to 5.70)	20.1	1.76 (0.88 to 3.55)
Highest tertile	97	47.1	6.42 (2.77 to 14.87)	23.9	3.91 (1.45 to 10.51)	30.7	2.70 (1.30 to 5.59)

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

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Flu-like symptoms and mental morbidities

In Figure 1, we present the proportions of individuals with flu-like symptoms lasting at least one week during the preceding two months among recovering COVID-19 patients, those who tested negative and those never tested for SARS-CoV-2 (more detailed in supplementary Table 6).

Individuals who tested negative reported 29-91% higher prevalence of symptoms than those never tested for SARS-CoV-2 (see supplementary Table 7), while individuals with a confirmed COVID-19 diagnosis had, compared to all others, dramatically increased adjusted risk ratios of all symptoms: 3.49 for gastrointestinal symptoms, 3.66 for myalgia, 4.16 for fatigue, 4.58 for sore throat, 4.64 for headache, 9.26 for shortness of breath, 19.10 for fever, and 32.52 for impaired sense of taste or smell (see supplementary Table 8).

We found that flu-like symptom burden was positively associated with symptom levels of depression, anxiety and PTSD, regardless of COVID-19 diagnosis (Figure 2 and supplementary Table 9). A stepwise increase across tertiles in flu-like symptom burden was associated with a rise in mean levels of depression, anxiety and PTSD among patients recovering from COVID-19, individuals who tested negative and those never tested for SARS-CoV-2. Recovering COVID-19 patients reporting low to medium flu-like symptom burden (low and mid tertiles) presented with lower levels of depression and anxiety compared to those with same levels of flu-like symptom burden but without a diagnosis of COVID-19 (Figure 2 and supplementary Table 9).

Finally, when flu-like symptom burden was added to the multivariable models (presented in Table 2), the direction of the adjusted relative risks of depression (0.63, 95% CI 0.51 to 0.77) and PTSD (0.73, 95% CI, 0.57 to 0.93) reversed in patients recovering from COVID-19 compared to others, indicating that flu-like symptoms mediated the risks of mental morbidity in this otherwise pre-pandemic healthy population.

DISCUSSION

The findings of this study suggest that patients recovering from COVID-19 may experience elevated risks of depression and PTSD, particularly if recovering from a severe disease. We found that mental morbidities among recovering COVID-19 patients were strongly associated with older age, higher educational level, greater flu-like symptom burden, extended time confined to bed and hospitalization due to COVID-19.

To our knowledge, this is the first study addressing mental morbidities among recovering COVID-19 patients in a general population setting, including outpatients. Our findings are in line with the vast literature reporting high rates of mental morbidities among current or discharged COVID-19 inpatients.[9, 10, 12, 13] Several mechanisms may play a role in the increased risk of mental health morbidities among patients recovering from a severe COVID-19 illness. These include worries and fear of infecting others, shame or stigma associated with being infected with COVID-19,[37] and uncertainty of the prognosis.[18] Indeed, the diagnosis of potentially life-threatening diseases, e.g. cancer, has previously been associated with a dramatic rise in risks of psychiatric disorders[38] and suicide.[39] In addition, dysregulated immune response, e.g. the documented cytokine storm associated with COVID-19,[40] may independently affect risks of psychiatric disorders in COVID-19 patients,[41] as has been documented in patients with other infections.[42] In line with Wang et al.,[43] we found that individuals with a higher educational level are more likely than those with a lower educational level to suffer from symptoms of depression and anxiety after a COVID-19 diagnosis. These findings are intriguing and require further investigation as previous studies have also provided contradicting results.[44]

Our mediation analysis suggests that flu-like symptom burden mediated the risk elevations in psychiatric morbidities among patients recovering from COVID-19. Moreover, flu-like symptoms among individuals without a confirmed COVID-19 diagnosis were also strongly associated with

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symptoms of mental morbidities, suggesting that the association is not limited to COVID-19. Indeed, COVID-19 patients reporting low-medium flu-like symptom burden, had lower levels of depression and anxiety than individuals without a diagnosis of COVID-19 but with similar levels of flu-like symptoms. While the healthy pre-pandemic profile of the COVID-19 population may be an indicator of psychological resilience during recovery from COVID-19, it is also possible that the systematic, daily surveillance calls to all COVID-19 patients from the specialized COVID-19 outpatient clinic at the National University Hospital had a positive mental health impact on patients.

This population-based study includes more than 20% of all patients diagnosed with COVID-19 by RT-PCR during the first wave of the epidemic in Iceland. The diagnostic rate in Iceland was among the highest worldwide during the first wave of the epidemic,[45, 46] allowing us to perform sensitivity analyses limited to individuals who all had been screened for SARS-CoV-2. The extensive and well-piloted questionnaire allowed us to obtain validated symptom assessment of mental morbidities along with detailed information on flu-like symptom burden for all individuals during the flu season in Iceland, together with a wide range of potential confounders in the association between COVID-19 and mental morbidities.

However, our study is cross-sectional and therefore less informative on the directionality of the studied associations. Indeed, a newly published study using data from the UK Biobank suggests that individuals with a history of pre-pandemic psychiatric disorders are more likely to be hospitalized and die from COVID-19.[47] Thus, it is possible that patients who were already experiencing psychological symptoms suffered the most severe COVID-19-related symptomology yielding the observed associations. However, we included previous diagnoses of psychiatric disorders in all our models which should, to some extent, alleviate this concern. Nevertheless, it is possible that individuals with severe symptoms of depression and anxiety were more likely to report high levels of flu-like symptoms during the preceding two months when responding to the questionnaire, yielding

a detrimental outcome-dependent misclassification. Indeed, the instrument to assess flu-like symptom burden included similar items (e.g. fatigue) as are included in the PHQ-9 instrument which, to some extent, could explain the association between COVID-19 and depression. Yet, more objective assessments of illness severity, e.g. the number of days confined to bed or hospitalized due to COVID-19 -- both of which were strongly associated with mental morbidities among patients - might to a lesser extent be influenced by the participants' mental status.

Participants recovering from COVID-19 may differ in terms of their mental health status from COVID-19 patients who did not participate in our study. While we were not able to disentangle the direction of such selection, our observed prevalence of depression and anxiety among recovering COVID-19 patients resembles prevalence rates recently reported in a meta-analysis of diverse COVID-19 patient populations elsewhere.[9] Finally, our study is nested within a small, economically and socially secure society with virtually free and high-quality health care for all, thus the findings may not be generalizable to other settings.

In conclusion, the relatively healthy first-wave COVID-19 population in Iceland presented with increased risk of depression and PTSD in the early weeks of recovery from their illness, particularly those recovering from a severe disease. These findings motivate further follow-up studies of mental health among patients recovering from COVID-19 and other serious infections, and heightened clinical surveillance of those recovering from a severe illness.

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Contributors: UV, TA, and JJ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. UV, AH, KSS, IM, JJ, TA conceived and design the study. UV, AH, KSS, IM, JJ, TA analysed the data, and all authors (KSS, HYH, IM, AH, EBT, ÁBG, GT, HR, HLJ, BG, GP, PHP, SYK, TJL, SH, HH, GG, EE, DGG, HS, SH, ADM, RP, JJ, TA, UV) interpreted the data. UV, KSS, HYH, IM drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. UV, AH, HR, GT, TA, JJ, SYK, TJL, SH, DGG, ADM provided administrative, technical, or material support. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: The original data and R codes are available on request upon approval of the National Bioethics Committee and the Data Protection Authority.

The lead author/guarantor of the study (UV) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure legends

Figure 1: The proportion of individuals with and without (tested and not tested) a confirmed
diagnosis of COVID-19 with flu-like symptoms of one week or more during the last two months
before responding to the baseline questionnaire.

Figure 2: Adjusted symptom scores of depression, anxiety and PTSD by flu-like symptom burden among individuals with a recent COVID-19 diagnosis, those who tested negative and those never tested for SARS-CoV-2.

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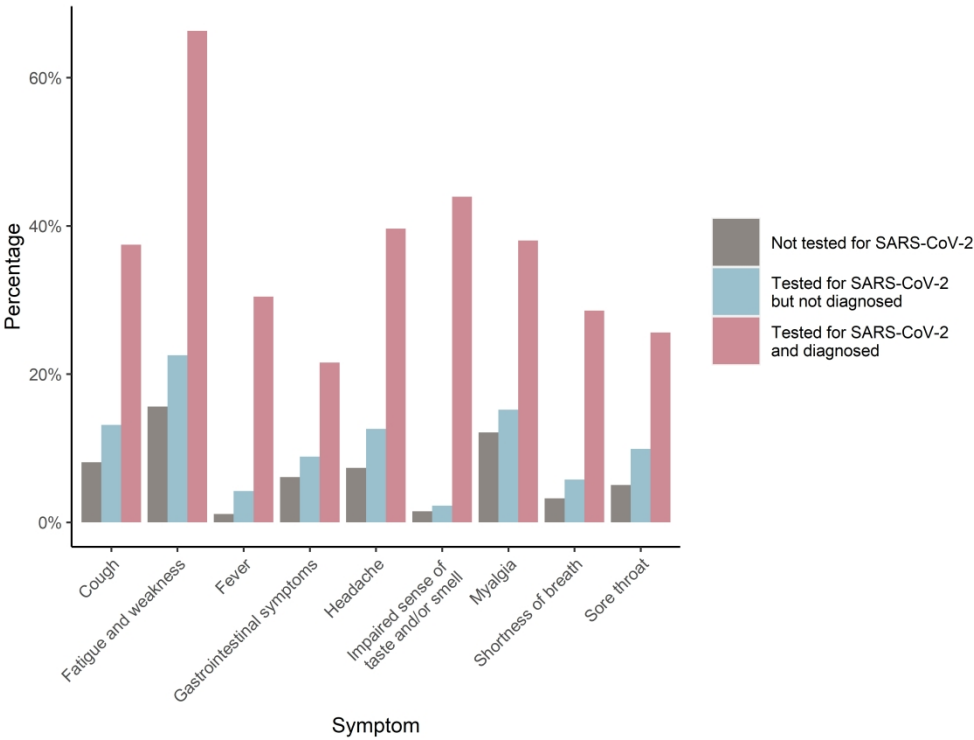


Figure 1 / The proportion of individuals with and without (tested and not tested) a confirmed diagnosis of COVID-19 with flu-like symptoms of one week or more during the last two months before responding to the baseline questionnaire.

203x152mm (600 x 600 DPI)

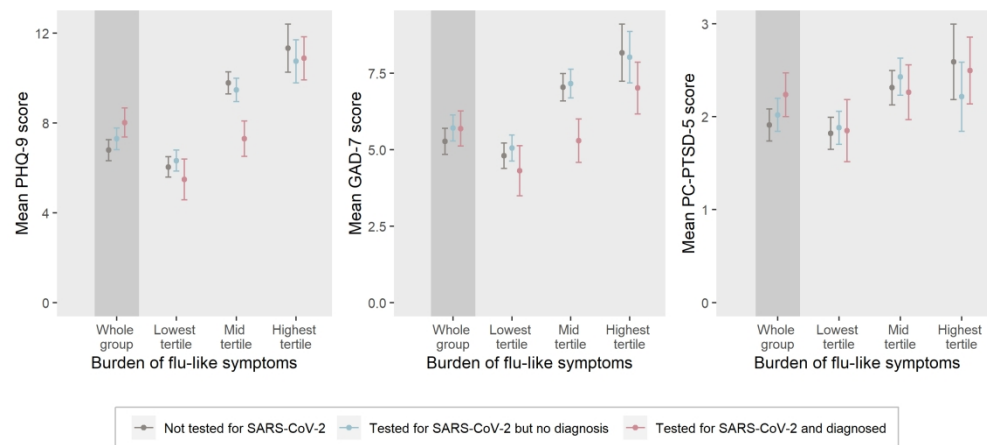
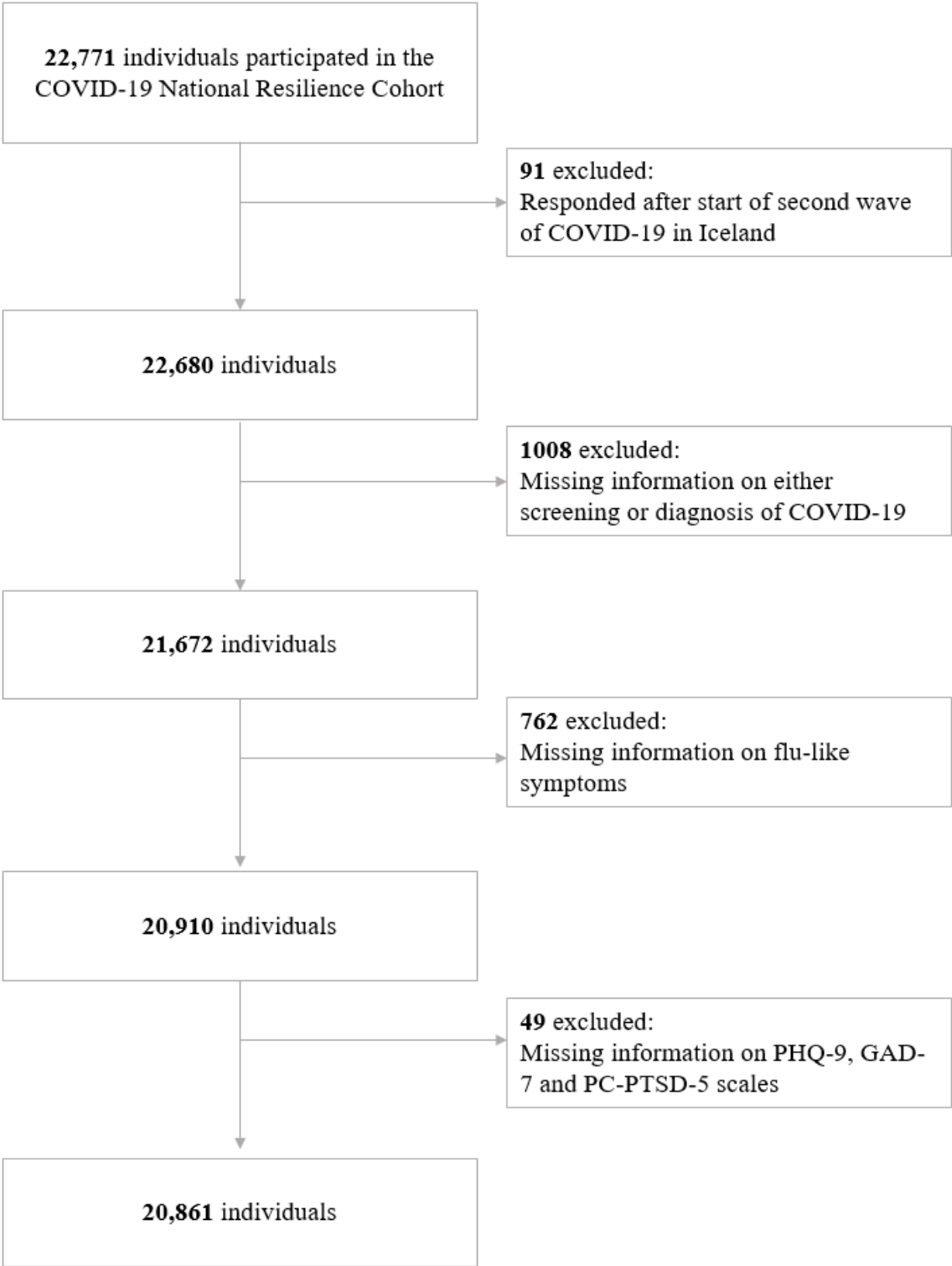


Figure 2 / Adjusted symptom scores of depression, anxiety and PTSD by flu-like symptom burden among individuals with a recent COVID-19 diagnosis, those who tested negative and those never tested for SARS-CoV-2.

254x127mm (300 x 300 DPI)

Supplementary material

Supplementary Figure 1. The analytic sample within the COVID-19 National Resilience Cohort.



Supplementary Table 1. Mean and median scores on PHQ-9, GAD-7, and PC-PTSD-5 among individuals with and without a recent COVID-19 diagnosis.

	Mean scores		Median scores		P-value	Adj. P-value
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19		
Depression	5.07	6.11	4	5	<.001	<.001
Anxiety	4.12	4.52	3	4	.07	.08
PTSD	1.72	1.90	2	2	.007	<.001

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

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Supplementary Table 2. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19. The data are presented with stratification of all covariates used in the multivariable adjusted models along with the p-values for the effect modification.

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference Crude %	Absolute difference Adjusted ^a %	P-value for effect modification
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19					
Depression	2992 (16.2)	75 (22.1)	1.36 (1.11 to 1.67)	1.48 (1.20 to 1.82)	5.9	8.4	
Female	2421 (18.8)	56 (24.8)	1.32 (1.05 to 1.66)	1.43 (1.13 to 1.81)	6.0	8.1	0.110
Male	559 (10.0)	17 (15.2)	1.52 (0.97 to 2.37)	1.54 (0.96 to 2.47)	5.2	7.2	--
18-39 years	954 (33.3)	23 (27.1)	0.81 (0.57 to 1.16)	0.94 (0.65 to 1.36)	-6.2	-1.8	0.025
40-59 years	1367 (16.8)	40 (22.3)	1.33 (1.01 to 1.75)	1.72 (1.31 to 2.27)	5.5	14.7	--
≥60 years	671 (8.9)	12 (15.8)	1.77 (1.05 to 2.98)	2.57 (1.52 to 4.36)	6.9	21.8	--
Compulsory education	540 (21.5)	6 (23.1)	1.07 (0.53-2.17)	1.24 (0.61-2.53)	1.6	4.7	<.001
Upper secondary, vocational or other education	996 (17.7)	15 (14.7)	0.83 (0.52-1.33)	0.83 (0.51-1.33)	-2.9	-2.5	--
Bachelor's degree or diploma certificate	935 (15.7)	30 (24.2)	1.54 (1.12-2.12)	1.56 (1.16-2.08)	8.5	10.2	--
Master's or Ph.D. degree	521 (11.9)	24 (27.3)	2.28 (1.61-3.24)	2.95 (2.03-4.29)	15.3	34.5	--
Low income	966 (29.8)	15 (31.3)	1.05 (0.69-1.60)	0.97 (0.61-1.55)	1.5	-0.8	0.059
Low-medium income	956 (18.1)	21 (25.3)	1.40 (0.96-2.04)	1.36 (0.97-1.89)	7.2	8.3	--
Medium income	637 (13.4)	18 (23.4)	1.75 (1.16-2.64)	1.66 (1.09-2.55)	10.0	12.6	--
Medium-high income	316 (9.3)	13 (15.1)	1.63 (0.98-2.72)	2.04 (1.24-3.35)	5.8	13.1	--
High income	117 (6.6)	8 (17.3)	2.64 (1.37-5.08)	2.90 (1.56-5.37)	10.8	15.3	--

Not current smoker	2351 (14.5)	71 (22.0)	1.52 (1.23-1.87)	1.53 (1.23-1.89)	7.6	8.0	0.234
Current smoker	641 (28.3)	4 (22.2)	0.79 (0.33-1.87)	0.91 (0.36-2.33)	-6.1	-1.6	--
No previous diagnosis of psychiatric disorder	1053 (8.0)	38 (14.6)	1.83 (1.36-2.47)	1.55 (1.13-2.12)	6.6	5.6	0.176
Previous diagnosis of psychiatric disorder	1939 (37.0)	37 (46.8)	1.27 (1.00-1.61)	1.36 (1.04-1.77)	9.9	13.6	--
No previously diagnosed somatic diseases	1776 (16.2)	54 (22.4)	1.38 (1.09-1.75)	1.52 (1.19-1.95)	6.2	7.7	0.923
1 previously diagnosed somatic disease	785 (14.6)	17 (20.7)	1.42 (0.92-2.18)	1.38 (0.91-2.10)	6.1	6.2	--
≥ 2 previously diagnosed somatic diseases	431 (19.8)	4 (23.5)	1.19 (0.50-2.81)	1.88 (0.70-5.06)	3.7	14.7	--
Response date: April 24-May 7	2206 (18.3)	45 (27.4)	1.50 (1.16-1.93)	1.62 (1.24-2.11)	9.1	12.6	0.531
Response date: May 8-July 22	786 (12.2)	30 (17.0)	1.40 (1.00-1.95)	1.24 (0.89-1.71)	4.9	3.2	--
Anxiety	2120 (11.3)	45 (13.1)	1.16 (0.88 to 1.53)	1.24 (0.93 to 1.64)	1.8	2.6	
Female	1759 (13.4)	34 (14.8)	1.11 (0.81 to 1.51)	1.17 (0.84 to 1.62)	1.4	2.2	0.007
Male	353 (6.2)	10 (8.9)	1.43 (0.78 to 2.60)	1.39 (0.76 to 2.54)	2.6	3.0	--
18-39 years	770 (26.2)	13 (14.9)	0.57 (0.34 to 0.95)	0.61 (0.36 to 1.04)	-11.3	-9.3	0.049
40-59 years	951 (11.5)	27 (14.7)	1.28 (0.90 to 1.82)	1.70 (1.20 to 2.41)	3.2	10.5	--
≥60 years	399 (5.2)	5 (6.9)	1.31 (0.56 to 3.06)	2.13 (0.91 to 5.00)	1.7	7.5	--
Compulsory education	378 (14.7)	2 (8.0)	0.54 (0.14-2.06)	0.75 (0.21-2.69)	-6.7	-2.7	0.009
Upper secondary, vocational or other education	690 (12.0)	11 (10.5)	0.87 (0.50-1.54)	0.84 (0.48-1.48)	-1.5	-1.4	--
Bachelor's degree or diploma certificate	658 (10.9)	17 (13.4)	1.23 (0.79-1.93)	1.18 (0.74-1.86)	2.5	2.0	--
Master's or Ph.D. degree	394 (8.9)	15 (17.2)	1.94 (1.21-3.11)	2.47 (1.53-3.99)	8.4	19.6	--
Low income	719 (21.6)	6 (12.5)	0.58 (0.27-1.23)	0.52 (0.24-1.12)	-9.1	-8.9	0.082
Low-medium income	657 (12.2)	17 (19.8)	1.62 (1.06-2.50)	1.44 (0.95-2.20)	7.6	6.6	--

Medium income	432 (8.9)	11 (14.5)	1.62 (0.93-2.82)	1.58 (0.89-2.81)	5.5	6.1	--
Medium-high income	223 (6.5)	9 (10.3)	1.60 (0.85-3.01)	2.05 (1.03-4.09)	3.9	8.0	--
High income	89 (5.0)	2 (4.3)	0.86 (0.22-3.38)	0.97 (0.25-3.73)	-0.7	-0.1	--
Not current smoker	1641 (10.0)	43 (13.2)	1.33 (1.00-1.76)	1.31 (0.98-1.76)	3.3	3.0	0.193
Current smoker	479 (20.6)	2 (10.5)	0.51 (0.14-1.90)	0.51 (0.13-1.98)	-10.1	-6.1	--
No previous diagnosis of psychiatric disorder	709 (5.3)	24 (9.2)	1.73 (1.18-2.55)	1.46 (0.97-2.19)	3.9	2.5	0.130
Previous diagnosis of psychiatric disorder	1411 (26.1)	21 (25.6)	0.98 (0.68-1.42)	1.03 (0.70-1.52)	-0.5	0.8	--
No previously diagnosed somatic diseases	1320 (11.9)	34 (13.9)	1.17 (0.85-1.60)	1.22 (0.88-1.71)	2.0	2.2	0.651
1 previously diagnosed somatic disease	519 (9.5)	10 (12.3)	1.30 (0.72-2.34)	1.31 (0.71-2.41)	2.9	3.0	--
≥ 2 previously diagnosed somatic diseases	281 (12.6)	1 (5.6)	0.44 (0.07-2.97)	0.75 (0.22-2.52)	-7.0	-2.7	--
Response date: April 24-May 7	1594 (13.0)	28 (16.7)	1.28 (0.91-1.80)	1.37 (0.97-1.94)	3.7	4.7	0.622
Response date: May 8-July 22	526 (8.0)	17 (9.7)	1.21 (0.76-1.91)	0.93 (0.57-1.52)	1.7	-0.6	--
PTSD	2699 (15.6)	59 (19.5)	1.25 (0.99 to 1.57)	1.38 (1.09 to 1.75)	3.9	7.2	
Female	2198 (18.6)	46 (22.7)	1.22 (0.94 to 1.58)	1.32 (1.02 to 1.71)	4.1	6.7	<.001
Male	493 (9.1)	12 (12.1)	1.33 (0.78 to 2.27)	1.60 (0.92 to 2.77)	3.0	7.1	--
18-39 years	597 (24.2)	11 (15.3)	0.63 (0.37 to 1.09)	0.77 (0.45 to 1.32)	-8.9	-6.2	0.003
40-59 years	1268 (16.7)	31 (19.3)	1.15 (0.84 to 1.59)	1.36 (0.99 to 1.88)	2.6	7.8	--
≥60 years	834 (11.6)	17 (24.3)	2.09 (1.38 to 3.18)	2.67 (1.78 to 4.01)	12.7	27.9	--
Compulsory education	367 (16.1)	7 (33.3)	2.08 (1.13-3.83)	2.41 (1.19-4.89)	17.2	24.8	0.239
Upper secondary, vocational or other education	809 (15.5)	20 (21.1)	1.36 (0.92-2.02)	1.44 (0.96-2.18)	5.6	9.1	--
Bachelor's degree or diploma certificate	912 (16.4)	23 (21.1)	1.29 (0.89-1.86)	1.34 (0.93-1.94)	4.7	4.8	--

Master's or Ph.D. degree	611 (14.7)	9 (11.5)	0.79 (0.42-1.46)	1.01 (0.55-1.84)	-3.1	0.2	--
Low income	602 (21.0)	10 (22.7)	1.08 (0.62-1.87)	1.11 (0.64-1.93)	1.7	2.2	0.756
Low-medium income	773 (15.8)	17 (23.6)	1.49 (0.98-2.27)	1.53 (0.98-2.37)	7.8	9.9	--
Medium income	726 (16.1)	12 (17.4)	1.08 (0.64-1.82)	1.16 (0.68-1.98)	1.3	2.8	--
Medium-high income	403 (12.3)	14 (17.9)	1.46 (0.90-2.36)	1.77 (1.14-2.76)	5.6	16.4	--
High income	195 (11.4)	6 (15.0)	1.32 (0.62-2.79)	1.53 (0.72-3.26)	3.6	6.7	--
Not current smoker	2244 (14.7)	51 (17.9)	1.22 (0.95-1.56)	1.28 (0.99-1.65)	3.2	4.5	0.054
Current smoker	455 (22.6)	8 (44.4)	1.97 (1.17-3.32)	2.83 (1.57-5.10)	21.9	37.4	--
No previous diagnosis of psychiatric disorder	1540 (12.2)	42 (17.6)	1.45 (1.10-1.92)	1.55 (1.17-2.06)	5.5	7.5	0.137
Previous diagnosis of psychiatric disorder	1159 (25.3)	17 (26.2)	1.04 (0.69-1.56)	1.11 (0.73-1.68)	0.9	3.0	--
No previously diagnosed somatic diseases	1611 (15.8)	41 (19.4)	1.23 (0.93-1.62)	1.44 (1.09-1.90)	3.6	7.6	0.325
1 previously diagnosed somatic disease	751 (14.8)	12 (16.0)	1.08 (0.64-1.82)	1.11 (0.66-1.87)	1.2	1.8	--
≥ 2 previously diagnosed somatic diseases	337 (16.7)	6 (35.3)	2.11 (1.10-4.04)	2.03 (0.94-4.40)	18.6	17.5	--
Response date: April 24-May 7	1996 (18.1)	32 (22.5)	1.25 (0.92-1.70)	1.24 (0.91-1.70)	4.5	5.8	0.256
Response date: May 8-July 22	703 (11.4)	27 (16.8)	1.47 (1.04-2.09)	1.41 (0.99-2.01)	5.4	6.0	--

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22). Adjustments are not made for the variable that is being stratified by.

Supplementary Table 3. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19 (*diagnosed at least two weeks before responding*).

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference	Absolute difference
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19			Crude	% Adjusted ^a %
Depression	2992 (16.2)	73 (22.0)	1.36 (1.11 to 1.67)	1.49 (1.20 to 1.84)	5.8	8.6
Female	2421 (18.8)	55 (24.9)	1.32 (1.05 to 1.67)	1.45 (1.14 to 1.83)	6.1	8.4
Male	559 (10.0)	16 (14.7)	1.47 (0.93 to 2.33)	1.52 (0.93 to 2.49)	4.7	6.9
18-39 years	954 (33.3)	22 (26.8)	0.81 (0.56 to 1.16)	0.95 (0.65 to 1.39)	-6.5	-1.5
40-59 years	1367 (16.8)	39 (22.3)	1.32 (1.00 to 1.75)	1.72 (1.30 to 2.28)	5.5	14.7
≥60 years	671 (8.9)	12 (16.0)	1.79 (1.06 to 3.02)	2.59 (1.53 to 4.39)	7.1	22.0
Anxiety	2120 (11.3)	45 (13.1)	1.16 (0.88 to 1.54)	1.25 (0.94 to 1.67)	1.8	2.9
Female	1759 (13.4)	33 (14.7)	1.10 (0.80 to 1.51)	1.17 (0.84 to 1.64)	1.3	2.3
Male	353 (6.2)	10 (9.1)	1.46 (0.80 to 2.67)	1.46 (0.80 to 2.64)	2.9	3.5
18-39 years	770 (26.2)	13 (15.5)	0.59 (0.36 to 0.98)	0.64 (0.38 to 1.09)	-10.7	-8.6
40-59 years	951 (11.5)	26 (14.4)	1.26 (0.88 to 1.80)	1.68 (1.18 to 2.41)	2.9	10.2
≥60 years	399 (5.2)	5 (6.9)	1.32 (0.57 to 3.10)	2.15 (0.91 to 5.03)	1.7	7.5
PTSD	2699 (15.6)	56 (18.9)	1.21 (0.95 to 1.54)	1.35 (1.06 to 1.73)	3.3	6.7
Female	2198 (18.6)	43 (21.7)	1.17 (0.89 to 1.53)	1.27 (0.97 to 1.67)	3.1	5.7
Male	493 (9.1)	12 (12.4)	1.36 (0.79 to 2.32)	1.64 (0.95 to 2.83)	3.3	7.5
18-39 years	597 (24.2)	10 (14.3)	0.59 (0.33 to 1.05)	0.72 (0.41 to 1.28)	-9.9	-7.4
40-59 years	1268 (16.7)	29 (18.5)	1.11 (0.79 to 1.54)	1.31 (0.94 to 1.84)	1.8	6.7
≥60 years	834 (11.6)	17 (24.6)	2.12 (1.40 to 3.23)	2.70 (1.80 to 4.05)	13.0	28.3

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22). Adjustments are not made for the variable that is being stratified by.

Supplementary Table 4. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19 (*using multiple imputation*).

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference	
	Individuals not diagnosed with COVID-19	Individuals diagnosed with COVID-19			Crude	% Adjusted ^a %
Depression	3487 (17.0)	83 (22.3)	1.31 (1.08 to 1.59)	1.44 (1.18 to 1.75)	5.3	8.1
Female	2819 (19.7)	64 (25.6)	1.29 (1.05 to 1.61)	1.43 (1.14 to 1.78)	5.9	8.3
Male	655 (10.7)	17 (14.1)	1.32 (0.85 to 2.08)	1.35 (0.85 to 2.16)	3.4	4.6
18-39 years	1105 (35.2)	26 (28.9)	0.82 (0.59 to 1.14)	0.95 (0.67 to 1.33)	-6.3	-1.8
40-59 years	1565 (17.5)	445(22.5)	1.29 (0.99 to 1.68)	1.68 (1.29 to 2.18)	5.0	14.8
≥60 years	817 (9.7)	12 (14.8)	1.52 (0.90 to 2.58)	2.23 (1.31 to 3.78)	5.1	17.2
Anxiety	2328 (11.3)	45 (12.1)	1.06 (0.81 to 1.40)	1.15 (0.87 to 1.53)	0.8	1.8
Female	1940 (13.5)	34 (13.6)	1.01 (0.73 to 1.38)	1.08 (0.78 to 1.50)	0.1	1.0
Male	378 (6.2)	10 (8.3)	1.34 (0.73 to 2.45)	1.34 (0.74 to 2.43)	2.1	2.6
18-39 years	830 (26.5)	13 (14.4)	0.55 (0.33 to 0.91)	0.61 (0.36 to 1.03)	-12.1	-10.0
40-59 years	1037 (11.6)	27 (13.6)	1.18 (0.83 to 1.68)	1.57 (1.11 to 2.23)	2.0	9.0
≥60 years	461 (5.5)	5 (5.9)	1.08 (0.46 to 2.53)	1.69 (0.72 to 3.97)	0.4	4.6
PTSD	2915 (15.8)	62 (19.2)	1.22 (0.97 to 1.53)	1.36 (1.08 to 1.71)	3.4	6.7
Female	2375 (18.7)	48 (22.1)	1.18 (0.92 to 1.52)	1.29 (1.00 to 1.66)	3.4	6.1
Male	532 (9.2)	13 (12.4)	1.34 (0.80 to 2.25)	1.57 (0.93 to 2.67)	3.2	6.9
18-39 years	642 (24.5)	11 (14.9)	0.61 (0.35 to 1.05)	0.71 (0.41 to 1.22)	-9.6	-7.9
40-59 years	1360 (16.8)	33 (19.3)	1.15 (0.84 to 1.57)	1.37 (1.00 to 1.87)	2.5	7.9
≥60 years	913 (11.8)	18 (23.1)	1.96 (1.30 to 2.96)	2.47 (1.65 to 3.69)	11.3	23.9

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22). Adjustments are not made for the variable that is being stratified by.

Supplementary Table 5. The prevalence, crude and multivariable adjusted relative risks and absolute differences in symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PC-PTSD-5) surpassing screening thresholds among individuals with and without a confirmed diagnosis of COVID-19 (*analysis limited to individuals who were tested for COVID-19*).

	No. (%)		cRR (95% CI)	aRR (95% CI) ^a	Absolute difference	
	Individuals that have been tested for COVID-19 but not diagnosed	Individuals that have been tested for COVID-19 and diagnosed			Crude	%
					Adjusted ^a %	
Depression	885 (19.4)	75 (22.1)	1.14 (0.92 to 1.40)	1.31 (1.06 to 1.62)	2.7	6.1
Female	712 (21.7)	56 (24.8)	1.14 (0.90 to 1.45)	1.30 (1.02 to 1.65)	3.1	6.2
Male	168 (13.2)	17 (15.2)	1.15 (0.72 to 1.82)	1.22 (0.75 to 1.97)	2.0	3.7
18-39 years	275 (37.6)	23 (27.1)	0.72 (0.50 to 1.03)	0.85 (0.58 to 1.23)	-10.5	-5.2
40-59 years	413 (17.8)	40 (22.3)	1.26 (0.94 to 1.68)	1.64 (1.23 to 2.17)	4.5	13.6
≥60 years	197 (13.1)	12 (15.8)	1.21 (0.71 to 2.07)	1.86 (1.09 to 3.18)	2.7	16.4
Anxiety	640 (13.8)	45 (13.1)	0.95 (0.72 to 1.26)	1.08 (0.81 to 1.44)	-0.7	1.1
Female	531 (15.9)	34 (14.8)	0.94 (0.68 to 1.29)	1.04 (0.75 to 1.45)	-1.1	0.6
Male	106 (8.2)	10 (8.9)	1.08 (0.58 to 2.01)	1.11 (0.60 to 2.04)	0.7	1.0
18-39 years	237 (31.3)	13 (14.9)	0.48 (0.29 to 0.80)	0.52 (0.31 to 0.89)	-16.4	-13.4
40-59 years	286 (12.1)	27 (14.7)	1.21 (0.84 to 1.75)	1.62 (1.13 to 2.31)	2.6	9.7
≥60 years	117 (7.7)	5 (6.9)	0.90 (0.38 to 2.12)	1.56 (0.66 to 3.70)	-0.8	5.1
PTSD	747 (17.8)	59 (19.5)	1.09 (0.86 to 1.39)	1.26 (0.99 to 1.60)	1.7	5.4
Female	626 (21.1)	46 (22.7)	1.08 (0.83 to 1.40)	1.19 (0.91 to 1.56)	1.6	4.5
Male	119 (9.7)	12 (12.1)	1.25 (0.71 to 2.17)	1.52 (0.86 to 2.67)	2.4	6.5
18-39 years	168 (27.6)	11 (15.3)	0.55 (0.32 to 0.97)	0.68 (0.39 to 1.18)	-12.3	-9.6
40-59 years	376 (17.4)	31 (19.3)	1.11 (0.80 to 1.54)	1.31 (0.94 to 1.83)	1.9	6.9
≥60 years	203 (14.2)	17 (24.3)	1.70 (1.11 to 2.63)	2.22 (1.46 to 3.37)	10.1	24.6

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22). Adjustments are not made for the variable that is being stratified by.

Supplementary Table 6. Raw prevalence of flu-like symptoms during the preceding two months among individuals with and without a recent COVID-19 diagnosis.

	No. (%)		P-value
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)	
No reported symptoms			
Yes	3023 (14.8)	12 (3.2)	<.001
No	17465 (85.2)	361 (96.8)	
Cough			
Never	13181 (64.3)	122 (32.7)	<.001
1-2 days	3658 (17.9)	57 (15.3)	
3-6 days	1734 (8.5)	55 (14.7)	
1-2 weeks	754 (3.7)	54 (14.5)	
Over 2 weeks	1161 (5.7)	85 (22.8)	
Fatigue and weakness			
Never	7535 (36.8)	32 (8.6)	<.001
1-2 days	6044 (29.5)	39 (10.5)	
3-6 days	3350 (16.4)	54 (14.5)	
1-2 weeks	1276 (6.2)	59 (15.8)	
Over 2 weeks	2283 (11.1)	189 (50.7)	
Fever			
Never	17362 (84.7)	127 (34.0)	<.001
1-2 days	1907 (9.3)	58 (15.5)	
3-6 days	831 (4.1)	74 (19.8)	
1-2 weeks	227 (1.1)	53 (14.2)	
Over 2 weeks	161 (0.8)	61 (16.4)	
Gastrointestinal symptoms			
Never	12589 (61.4)	162 (43.4)	<.001
1-2 days	4565 (22.3)	69 (18.5)	
3-6 days	1941 (9.5)	61 (16.4)	
1-2 weeks	585 (2.9)	42 (11.3)	
Over 2 weeks	808 (3.9)	39 (10.5)	
Headache			
Never	8583 (41.9)	73 (19.6)	<.001
1-2 days	6754 (33.0)	57 (15.3)	
3-6 days	3381 (16.5)	95 (25.5)	
1-2 weeks	816 (4.0)	62 (16.6)	
Over 2 weeks	954 (4.7)	86 (23.1)	

	No. (%)		P-value
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)	
Impaired sense of taste and/or smell			
Never	19514 (95.2)	140 (37.5)	<.001
1-2 days	411 (2.0)	25 (6.7)	
3-6 days	220 (1.1)	44 (11.8)	
1-2 weeks	111 (0.5)	55 (14.7)	
Over 2 weeks	232 (1.1)	109 (29.2)	
Myalgia			
Never	12253 (59.8)	105 (28.2)	<.001
1-2 days	3512 (17.1)	54 (14.5)	
3-6 days	2072 (10.1)	72 (19.3)	
1-2 weeks	708 (3.5)	81 (21.7)	
Over 2 weeks	1943 (9.5)	61 (16.4)	
Shortness of breath			
Never	17111 (83.5)	169 (45.3)	<.001
1-2 days	1809 (8.8)	42 (11.3)	
3-6 days	775 (3.8)	55 (14.7)	
1-2 weeks	312 (1.5)	41 (11.0)	
Over 2 weeks	481 (2.3)	66 (17.7)	
Sore throat			
Never	12987 (63.4)	153 (41.0)	<.001
1-2 days	4323 (21.1)	62 (16.6)	
3-6 days	1901 (9.3)	63 (16.9)	
1-2 weeks	632 (3.1)	39 (10.5)	
Over 2 weeks	645 (3.1)	56 (15.0)	

Supplementary Table 7. Prevalence, crude and adjusted relative risks with 95% confidence intervals of flu-like symptoms lasting for 1 week or more, during the preceding two months, among individuals who tested negative for SARS-CoV-2 and those who were never tested.

Symptoms	No. (%)		cRR (95% CI)	aRR (95% CI) ^a
	Individuals not tested for SARS-CoV-2 (n = 15442)	Individuals tested negative for SARS-CoV-2 (n = 5046)		
Cough	1249 (8.1)	666 (13.2)	1.60 (1.46 to 1.76)	1.59 (1.45 to 1.75)
Fatigue and weakness	2420 (15.7)	1139 (22.3)	1.45 (1.36 to 1.55)	1.37 (1.29 to 1.46)
Fever	176 (1.1)	212 (4.2)	3.71 (3.02 to 4.56)	3.49 (2.84 to 4.29)
Gastrointestinal symptoms	946 (6.1)	447 (8.9)	1.48 (1.33 to 1.66)	1.37 (1.23 to 1.53)
Headache	1134 (7.3)	636 (12.6)	1.74 (1.58 to 1.91)	1.60 (1.46 to 1.75)
Impaired sense of taste or smell	229 (1.5)	114 (2.3)	1.53 (1.21 to 1.93)	1.64 (1.30 to 2.07)
Myalgia	1881 (12.2)	770 (15.3)	1.26 (1.16 to 1.36)	1.29 (1.19 to 1.39)
Shortness of breath	503 (3.3)	290 (5.7)	1.88 (1.62 to 2.17)	1.84 (1.59 to 2.13)
Sore throat	778 (5.0)	499 (9.9)	1.98 (1.77 to 2.21)	1.91 (1.71 to 2.14)

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 8. Prevalence, crude and adjusted relative risks with 95% confidence intervals of flu-like symptoms lasting for 1 week or more, during the preceding two months, among individuals with and without a confirmed diagnosis of COVID-19.

Symptoms	No. (%)		cRR (95% CI)	aRR (95% CI) ^a
	Individuals not diagnosed with COVID-19 (n = 20488)	Individuals diagnosed with COVID-19 (n = 373)		
Cough	1915 (9.4)	139 (37.3)	4.15 (3.60 to 4.76)	5.02 (4.35 to 5.81)
Fatigue and weakness	3559 (17.4)	248 (66.5)	3.93 (3.63 to 4.26)	4.16 (3.77 to 4.60)
Fever	388 (1.9)	114 (30.6)	16.77 (13.93 to 20.19)	19.10 (15.49 to 23.48)
Gastrointestinal symptoms	1393 (6.8)	81 (21.7)	3.29 (2.69 to 4.06)	3.49 (2.82 to 4.32)
Headache	1770 (8.6)	148 (39.7)	4.67 (4.10 to 5.37)	4.64 (3.99 to 5.39)
Impaired sense of taste or smell	343 (1.7)	164 (44.0)	27.04 (23.10 to 31.82)	32.52 (27.22 to 38.86)
Myalgia	2651 (12.9)	142 (38.1)	3.03 (2.65 to 3.49)	3.66 (3.16 to 4.23)
Shortness of breath	793 (3.9)	107 (28.7)	7.53 (6.05 to 9.03)	9.26 (7.61 to 11.25)
Sore throat	1277 (6.2)	95 (25.5)	4.17 (3.46 to 5.00)	4.58 (3.78 to 5.54)

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Supplementary Table 9. Adjusted mean symptom scores of depression, anxiety and PTSD by flu-like symptom burden in tertiles among individuals with a recent COVID-19 diagnosis, those who tested negative and those never tested for SARS-CoV-2.

	Multivariable adjusted mean value by tertile of flu-like symptoms ^a			Beta (95% CI)	P-value
	Lowest tertile	Mid tertile	Highest tertile		
Depression					
Patients with COVID-19	5.49	7.30	10.89	0.24 (0.17 to 0.30)	<.001
Tested negative for SARS-CoV-2	6.33	9.48	10.75	0.29 (0.25 to 0.33)	<.001
Not tested for SARS-CoV-2	6.04	9.79	11.34	0.34 (0.33 to 0.36)	<.001
Anxiety					
Patients with COVID-19	4.31	5.29	7.02	0.12 (0.06 to 0.17)	<.001
Tested negative for SARS-CoV-2	5.06	7.16	8.02	0.19 (0.16 to 0.23)	.03
Not tested for SARS-CoV-2	4.81	7.04	8.17	0.22 (0.20 to 0.23)	<.001
PTSD					
Patients with COVID-19	1.85	2.26	2.50	0.03 (0.01 to 0.05)	<.001
Tested negative for SARS-CoV-2	1.88	2.43	2.21	0.05 (0.04 to 0.06)	.02
Not tested for SARS-CoV-2	1.82	2.31	2.59	0.06 (0.06 to 0.07)	<.001

^a Adjusted for age (continuous variable), gender (male, female, or other), educational level (compulsory education, high school/trade school/other education, bachelor's degree/diploma certificate, or master's/Ph.D. degree), income (continuous variable), current smoking (yes or no), previous diagnosis of a psychiatric disorder (yes or no), number of previously diagnosed somatic diseases (0, 1, or ≥ 2), and timing of responding to the baseline questionnaire (April 24-30, May 1-7, May 8-23, or May 24-July 22).

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectional reporting guidelines, and cite them as: von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

Reporting Item		Page Number
Title and abstract		
Title	#1a Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction		
Background / rationale	#2 Explain the scientific background and rationale for the investigation being reported	6
Objectives	#3 State specific objectives, including any prespecified hypotheses	7
Methods		
Study design	#4 Present key elements of study design early in the paper	7-8

1	Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
2				
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6	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7-8
7				
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10		#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
11				
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13				
14				
15	Data sources /	#8	For each variable of interest give sources of data and details of methods of assessment (measurement).	8-10
16	measurement		Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
17				
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23	Bias	#9	Describe any efforts to address potential sources of bias	19-20
24				
25				
26	Study size	#10	Explain how the study size was arrived at	7-8
27				
28	Quantitative	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8-10
29	variables			
30				
31				
32				
33	Statistical	#12a	Describe all statistical methods, including those used to control for confounding	10-11
34	methods			
35				
36				
37	Statistical	#12b	Describe any methods used to examine subgroups and interactions	10-11
38	methods			
39				
40				
41	Statistical	#12c	Explain how missing data were addressed	11
42	methods			
43				
44				
45	Statistical	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
46	methods			
47				
48				
49	Statistical	#12e	Describe any sensitivity analyses	10-11
50	methods			
51				
52				
53	Results			
54				
55	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing	12-14
56				
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60				

		follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	7-8 (addressed in the methods chapter)
Participants	#13c	Consider use of a flow diagram	Supplementary material: page 1, Supplementary Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12-14
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	7-8 (addressed in the methods chapter)
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	14-17
Main results	#16a	Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-16
Main results	#16b	Report category boundaries when continuous variables were categorized	9-10 (addressed in the methods chapter)
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14-16
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	#18	Summarise key results with reference to study objectives	18
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19-20

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	18-20
Generalisability	#21	Discuss the generalisability (external validity) of the study results	20
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

Notes:

- 13b: 7-8 (addressed in the methods chapter)
- 13c: Supplementary material: page 1, Supplementary Figure 1
- 14b: 7-8 (addressed in the methods chapter)
- 16b: 9-10 (addressed in the methods chapter)

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